Multimorbidity in a general practice population

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prevalence, incidence and determinants of multiple pathology

The study presented in this thesis was conducted at the Research Institute for Extramural and Transmural Health Care (ExTra), which participates in the Netherlands School of Primary Care Research (CaRe), acknowledged in 1995 by the Royal Dutch Academy of Science (KNAW).

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Uil legde uit dat in geval van Plotselinge
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CONTENTS

CHAPTER 1

INTRODUCTION

MOTIVE FOR THE STUDY

Doctors often wonder about the differences in susceptibility for disease as they see some patients getting disease upon disease, while others rarely visit their doctor and seem to live without disease. An increasing number of people is suffering from multiple diseases, also called multimorbidity. This is a phenomenon of population wide magnitude. Both chronic and acute diseases have a high impact on patients' quality of life[1-3], as well as on physical and social disability[4-6]. The lives of direct caregivers can change considerably as a result of disease of a family member[7]. Besides, diseases result in high costs to society, because of the direct relationship between diseases and the use of health care services[8-12], as well as a loss of productivity[13]. The nature of occurring diseases has changed dramatically: there is an increasing prevalence of non-fatal diseases, as a consequence of ageing of the population and increasing medical knowledge and medical technology. As a result mortality rates are far below morbidity rates and the number of people with chronic disease and disability is rising[14]. In the daily practice of health care, the change to more chronic and multiple pathology is obvious. Especially the GP is often confronted with complex health situations, because of his pivot function in health care: working as a gate-keeper, delivering continuous care to the patients and receiving medical reports after referrals to other health care providers. Considering this, it is not surprising that causal factors of health and disease are major areas of research.

Medical research can be split into several divisions that match with the different aspects of clinical practice: prevention, diagnosis, natural course of disease, aetiology, and therapy. Research on aetiologies has mainly focused on causes of specific diseases or specific combinations of diseases. This has revealed innumerable relevant results with many consequences for the actual health care practice. However, evaluating 50 years of epidemiological research in the area of coronary heart disease, Syme[15] concluded this has yielded a number of disease specific aetiologies, that together explain only about 40% of the coronary heart diseases that occur, leaving 60% unaccounted for. Another illustrative fact of the limitedness of an exclusive disease specific approach is that, although the main causes of death have changed considerably over time, morbidity and mortality rates seem rather stable over socio-economic classes over a long time

period. Furthermore, even if disease specific aetiologies are known, it is often not clear what makes some persons with a certain risk factor more susceptible than others who have the same risk factor. This can also be expressed in terms of the intensity and variability issue. The intensity issue is the problem why some people become ill when exposed to adverse circumstances, while others do not. The variability issue applies to why susceptible people who have similar life experience develop different types of illness[16]. This implies that susceptibility to a wide range of diseases might be influenced by general risk factors rather than specific factors alone[17]. Inequities in health are quite extensively studied in relation to the socio-economic and demographic differences within populations[18-22]. It is considered common knowledge now that people with a lower educational level, and lower income have higher risks of getting diseased[21 23 24] and have shorter life expectancies[21 25 26]. It has been suggested that - apart from socio-economic and demographic factors - especially psychological and sociological features (like coping styles, life events, health locus of control, social network) might influence disease susceptibility[27-29]. Epidemiological studies in Western industrialised societies generally assume that host response mechanisms - coping style, individual biology, social resources available to the individual - operate only at the level of the individual. Cross-cultural research suggests however, that these factors also have an important influence at a population level[30].

In conclusion it seems useful to evaluate the influence of more general characteristics on disease susceptibility, i.e. to focus on personal factors and characteristics and their relation with multimorbidity rather than on disease specific aetiologies. This can serve to improve risk profiles of patients, and may facilitate the development of future preventive interventions as well as a better monitoring of patients.

Throughout this thesis the following key questions will be answered:

- How can comorbidity and multimorbidity be defined and operationalized?
- What are the main relevant methodological and analytical issues with respect to research on comorbidity and multimorbidity?
- What are the incidence and prevalence rates of multimorbidity in the general population?

- What are the major determinants of multimorbidity, with specific focus on demographic and psycho-social and life style characteristics?

OUTLINE OF THIS THESIS

Chapter 2 includes a literature review on the co-occurrence of diseases. First, differences in terms and definitions used in this field of research are described. The use of an unambiguous terminology is proposed, distinguishing between comorbidity and multimorbidity. Furthermore, a summary of previous studies regarding the occurrence, consequences, possible explanations and causes of comorbidity and multimorbidity is supplied. In *chapter 3* methods and strategies for analysing comorbidity and multimorbidity are discussed and illustrated. In *Chapter 4* the results of a secondary analysis of data regarding over 60,000 patients from the Registration Network Family Practices are reported. The main points of interest in this chapter are the incidence and prevalence rates of multimorbidity, as well as the relation between multimorbidity and socio-demographic characteristics. *Chapter 5* deals with the results of a nested case-control study, discussing demographic, psychological and sociological characteristics and the associations with multimorbidity. The response and non-response analysis of the case-control study is extensively described in *chapter 6*. The two-year follow-up of this population and results of the prospective study, focusing on psycho-social characteristics, are reported in *chapter 7*. *Chapter 8* provides a general discussion of the methods, sample and population, results and conclusions of all studies. Finally, in *chapters 9 and 10* summaries, in English and in Dutch respectively, are provided.

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CHAPTER 2

COMORBIDITY OR MULTIMORBIDITY: WHAT'S IN A NAME?

A review of literature

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Comorbidity or multimorbidity: what's in a name? A review of literature.

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ABSTRACT

Aim: Comorbidity is increasingly prevalent. Moreover, many different definitions and interpretations of this phenomenon are used. Because of its social and clinical significance, it is important that the concept is clear. In this review, a summary of the current uses of this concept and relevant figures are given, as well as a proposal for future use.

Method: A computerized search and an additional literature search were performed to identify relevant papers on comorbidity and related subjects. Available literature on the subject (n=38) was reviewed on definition, occurrence and potential determinants.

Results: The definitions in use are ambiguous; while some just imply coexistence of several diseases, others require medical conditions additional to an index disease. Other differences are related to the population and number of diseases under study.

Reported prevalence of comorbidity varies from less than 1% to over 50%, with higher prevalence among the elderly. Consequences such as disability and decreased quality of life are reported for the individual. There are also effects on the family and close friends which can be expressed in the social prevalence of disease. In addition there are consequences for the economy and health care. Explanations for observed comorbidity include causal mechanisms, bias and a general susceptibility for disease.

Discussion: Since the introduction of the term comorbidity about 30 years ago, the concept has been used in many different ways. Because of the ambiguity of the term, we suggest a distinction between comorbidity based on the 'classical' definition (implying an index disease) and multimorbidity, meaning any co-occurrence of medical conditions within one person.

INTRODUCTION

Comorbidity was originally perceived as the occurrence of medical conditions additional to an index disease[1]. Some authors, however, have a much broader definition, only implying the coexistence of diseases as such.

During the last few decades there has been growing interest in studies on comorbidity, probably due to the fact that it is causing more and more problems. Comorbidity is common and in many cases it is a heavy burden on the patient[2-5]. The degree of disability, for example, increases with the number of conditions the patient is suffering from[3], and comorbidity is associated with a frequent use of health care services with important economic consequences[6-8]. The phenomenon comorbidity is of special interest to general practice, where a broad spectrum of morbidity is covered rather than there being a focus on specific disease categories. In the Netherlands the general practitioner (GP) is a gatekeeper to other health care facilities. Patients visit their own GP before possible referral to specialist care. As a result the GP will be directly confronted with the effects of (an increasing prevalence of) co-occurring diseases. Furthermore, the GP in particular has the task and the opportunity of handling the complex health situation of co-occurring diseases, the subsequent treatment and effects of both on daily life.

The number of people suffering from more than one chronic condition at a time is expected to rise. Co-occurrence of chronic conditions is more common among the elderly[2 6 7 9-12], and the proportion as well as the number of old people will increase. For example, in 1990, 12% of the Dutch population were 65 years and older. By the year 2025 this is expected to be 21%. Also within the age group of 65 and over, people are living longer and longer[13]. Comorbidity has been studied in many different settings, in different population groups, using different definitions and different measures. As a result there is no generally accepted concept of comorbidity. Because of the clinical and social relevance of comorbidity, our aim is to contribute to the concept and its implications.

In this paper the results of a literature review on comorbidity and related concepts are reported. The principal questions are:

1. Which concepts and definitions are used by the various authors? What does the term

comorbidity imply according to them? What are other relevant terms to describe the concept?
2. What are the incidence and prevalence of comorbidity as reported in the various studies?
3. What are the effects of comorbidity on patients, family and society, as reported in these studies?
4. What explanations are given for the occurrence of comorbidity?

METHODS

Retrieval of literature

Literature was located initially by a computer search on Medline (CD-rom) for the period 1966-1994. Four search criteria were used in free text: comorb*, multimorb*, polypath* and disease susceptibility. Other expressions, such as 'multiple pathology', 'multiple disorder' and 'vulnerability' proved impractical, since they yielded too many titles without specifically identifying comorbidity and related concepts. Searches in Exerpta Medica and FAMLI with similar criteria did not yield extra articles, and will therefore not be discussed. In addition, the references of all selected papers were carefully screened until no new literature was found (ancestry approach), and experts in the field were contacted.

Selection of literature

Literature was selected for this review if it was based on a study of empirical data, concerning comorbidity, multimorbidity or related concepts or if it reported on theoretical concepts related to comorbidity, multimorbidity or general disease susceptibility. In this review we focused on comorbidity covering a broad nosological spectrum. Therefore, articles in which the object of the study was either one index disease or a particular combination of two or more diseases were not included in the review. However, concepts used in such articles were reviewed, if they represented a supplementary view.

Data extraction

All available papers were screened for explicit definitions as well as implicit descriptions which could be derived from the text. Furthermore, literature was evaluated on prevalence and incidence

rates, the effects of co-occurring diseases on the patient, the family and close friends and on society. Finally, we looked for descriptions or explanations for co-occurrence of diseases. These are classified into causes, methodological bias and other explanations.

RESULTS

Efficiency of the search

Comorbidity was first included as a MeSH-term in 1989. Our primary Medline search (1966-1994) using 'comorb*', 'multimorb*' and 'polypath*' as key words supplied 12 relevant articles for this review[3 4 6 8-10 15-20]. Another 16 publications [1 2 5 7 11 12 14 30 32-39] were found by means of the ancestry approach. The key word 'disease susceptibility' in Medline (1966-1994) yielded 8 papers[21-28], 2 more publications were found following the ancestry approach[29 31].

The key word comorb* located many more papers which were not included, because they were focused on one index disease or a specific combination of diseases. Many of them dealt with psychiatric comorbidity, including depression, abuse, alcohol and drugs. Other articles focused on AIDS and HIV, hypertension, infectious diseases, kidney disorders and myocardial infarctions. Finally, a total of 38 publications on comorbidity, multimorbidity, polypathology and general disease susceptibility were selected for this review[1-12 14-39].

Definition

The word comorbidity is relatively new in medicine. Less than 30 years ago, Feinstein was the first to use the term[39]. He described it in terms of 'an associated illness arising from other diseases'. He later defined it as 'any distinct additional entity that has existed or may occur during the clinical course of a patient who has the index disease under study'[1]. Since then, the concept has evolved in different directions[2 3 7 11 12 16 18 19 34 35 38]. All definitions assume the co-occurrence of states or situations related to health.

Differences are either explicitly defined or emerge implicitly through operationalization of research questions; diseases and conditions studied vary, as do the study populations. With respect to the number and type of diseases and conditions studied, the following can be distinguished:

- a limited number of particular diseases or conditions[2 3 11 12 17] versus no limits on the type and number of conditions[4 16 18 30 34 36 37];
- only chronic conditions[2 3 11 12 16 36 37] versus both chronic and acute diseases[4 17 18 30 34];
- only somatic diseases[2-4 11 17] versus somatic and psychiatric or social disorders[12 16 18 30 36 37];
- only diseases and conditions diagnosed by a physician[4 12 16 18 30 36 37] versus all problems or conditions reported by the patient himself[2 3 11 17].

With respect to the populations studied, a similar phenomenon can be observed. Restrictions concerning the populations may be:

- only patients who visit the general practitioner[4 16 34 36-38] versus only patients who are admitted into hospital[18 30] versus populations selected on aspects other than being a patient in a specific setting[2 3 11 12 17 19 29 32 33];
- only patients of a certain age group[2-4 11 12 16-19 29] versus patients of all ages[30 32-38].

The enormous differences in the age groups under study particularly complicated the comparison of results.

Some authors have introduced other terms to describe the same or closely related concepts. One alternative term is 'polypath(olog)y' or 'polymorbidity'. However, this term has several linguistic connotations. In German studies[6 9 10], polypathy is defined as 'the co-occurrence of several infirmities (of old age) or complaints'. On the other hand, in a French study polypathology is defined as 'the co-occurrence of conditions that are related to one another', as opposed to comorbidity where conditions would not interact[18]. An example of polypathology in these terms is 'pathologie en cascade' which is a chain of diseases/conditions resulting from the same origin. Another term 'multimorbidität' (or 'multimorbidity') is used in several German studies[6 9 10 20], meaning 'the co-occurrence of several chronic or acute diseases'.

Attempts have been made to classify or categorize the various meanings of the word comorbidity. Schellevis used a classification with 4 categories[38]:

- concurrent comorbidity: the coexistence of diseases in the same person without any satisfactory explanation, e.g. cardiovascular disease and osteaorthritis;

- cluster comorbidity: the distribution of diseases in a population showing concentrations in subgroups that differ significantly from a random distribution;
- causal comorbidity: interrelation of diseases based on a proven common pathophysiological cause, e.g. ischaemic heart disease and peripheral arterial disease;
- disease-specific complicating comorbidity: the existence of one disease is a requisite for the occurrence of another disease, e.g. diabetes mellitus and diabetic retinopathy.

This is a sensible classification, but not all categories are mutually exclusive and they represent various dimensions.

Occurrence

Although the collected studies are different in many respects, table 1 gives an impression of some results regarding the prevalence of co-occurrence of medical conditions. Recognising all differences in design and definition, it is clear that the co-occurrence of diseases is a common phenomenon. Two or more conditions are reported in less than 1% [38] to over 50% of the studied populations[2 4 12]. Furthermore several studies reported a sharp rise in the prevalence and incidence of co-occurring diseases with increasing age[2 11 30 37 38].

Effects of co-occurring diseases

Co-occurrence of diseases affects the patient, the people close to him, and society. Furthermore, consequences in all these categories may influence the use of health care facilities. There may be profound implications for the individual. Several studies show that it is related to physical as well as social disability[2 3 7 16 17]. In all ages the average grade of disability rises with the number of conditions, but in the elderly this relationship is even stronger[2]. Co-occurrence of diseases may result in pain and suffering, disability, loss of independence and deterioration in the quality of life[5]. Improvements in medical technology have resulted in people with (multiple) chronic conditions living longer without being cured[5]. Furthermore, specific combinations of diseases may have a significant impact on life expectancy. Moreover, the number of conditions suffered is associated with the chances of getting another disease. A cross-sectional analysis shows that the probability of having at least one more chronic disorder rises with the number of concurrent

TABLE 1: Summary of empirical studies on comorbidity, multimorbidity, and related concepts*

author(s)	original subject of the study	setting	population	number of conditions studied	results regarding co-occurring diseases
Guralnik et al[2], USA	the prevalence and co-prevalence of common chronic conditions	self-reported in Supplement on Aging of the National Health Interview Survey	people aged 60 years and over N = 13,807	9	number exp. % obs. % 0 21.2 13.9 1 30.1 34.7 ≥2 48.7 51.4
Verbrugge et al[3], USA	influence of the number and kind of chronic diseases on social and physical handicap	self-reported in Supplement on Aging of the National Health Interview Survey	people aged 60 years and over N=13,807	13	number % 0 16.4 1 20.5 ≥ 2 63.1
Parkerson et al[4], USA	development of a severity of illness measurement	ambulatory patients visiting a family medical centre. Demographic questionnaire by the patient, health problems listed by physician	18-65 years N ≈ 3,000	∞**	mean number of problems per patient: 1.94 number % 1 47.6 ≥ 2 52.4
Seeman et al[11], USA	consequences of comorbidity with respect to mortality, onset of new morbidity, and depression	Alameda County Study; questionnaire on behavioural, social and psychological aspects of life and a self-reported health status	≥38 years in 1965 N = 4,174	22	age 38-59 ≥60 number % % 0 34.9 23.8 1 22.2 20.3 ≥2 42.9 55.9
Deeg et al[12], the Netherlands	hypothesis of synergetic interaction	Dutch Longitudinal Health Survey reported by general practitioner (GP)	basic population 65-99 years in 1955-1957 N = 3,149	10	number % 0 19 1 27 ≥2 54
Meyboom-de Jong[16], the Netherlands	morbidity and functional status of the elderly patient	diagnosed by the GP	patients aged 65 years and over visiting the GP N = 5,500	∞	number % 0 55 1 26 ≥2 19
Newacheck et al[17], USA	prevalence and impact of chronic conditions among adolescents	self-reported in National Health Survey on Child Health	adolescents aged 10 to 17 years N = 7,465	∞	number % 0 68.5 1 21.3 ≥2 10.2

Saint-Jean et al[18], France	testing the clustering of morbidity	hospitalised patients at a geriatric ward	80 years and over N = 100	∞	polypathology: 76% comorbidity: 24%
Wilson et al[30], United Kingdom	what factors influence development of disability? Is the single diagnosis correct? Is it correct to adopt the common device of selecting a single 'main diagnosis' to represent the disability?	all patients entering a geriatric unit	mostly aged 65 and over, some younger patients with chronic disabilities N = 200	∞	number % 1-3 21.5 ≥4 78.5
IJzermans and Oskam[34], the Netherlands	what is the amount of clustering in time within patients and within family? Influence of sex, age and being a family member	data collected in general practice	data from the Monitoring project, N = 16,209, and the Transition project (40,796 patient-years)	∞	contacts and new diagnosis cluster in almost 25% of the patients
Knottnerus et al[36], the Netherlands	study on prevalence and social prevalence of chronic diseases to estimate the epidemiological and social burden of illness, and the relation with age, gender, level of education, and type of insurance	problems registered by the GP	population of Registration Network Family Practices, March 1990 N = 25,357; all ages.	83	number % 0 70.7 1 20.0 ≥2 9.3
Metsemakers et al[37], the Netherlands	description of objectives and methods of a registration network of family practices and initial analysis of data	problems registered by the GP	all ages, N = 32,972	∞	mean number of active problems age males females 0-14 0.5 0.4 5-14 0.7 0.6 15-24 0.8 0.9 25-44 1.2 1.4 45-64 2.1 2.3 65-74 3.0 3.2 75+ 3.5 4.1 total 1.4 1.7
Schellevis[38], the Netherlands	describing the extent of comorbidity of chronic diseases in general practice in the Netherlands	diagnosed by GP	all ages, N = 23,534	5	number <65 ≥65 % % 0 95.9 76.9 1 3.8 19.5 ≥ 2 0.3 3.6

* In this table terms and definitions are maintained as used in the original studies

** ∞ means that no diagnoses are excluded

conditions[36]. Seeman et al[11] reports similar findings on longitudinal data; a significant relationship between the number of conditions at baseline and new morbidity was found in all age groups.

Not only the patient suffers from multiple pathology. The co-occurrence of diseases is embedded in the social context of the circle of family and friends. In this respect Knottnerus et al[36] introduced the concept of social prevalence, meaning that more people are involved with the disease than just the patients themselves. The effects on patients' families and other care providers are also mentioned by Rice et al. Caring for somebody with multiple disorders may take a lot of time and energy and carers may be forced to change their lifestyles and, for example, forgo job opportunities. Moreover, the burden on society will increase as people live longer in a disabled state, creating an even greater need for social services[5]. In addition, the cost to society is substantial in medical and health care expenses and in loss of productivity[5 7 8].

Explanations for co-occurrence of diseases

Most research on causes of diseases has focused on specific diseases or combinations of them. Only a small number of studies provide hypotheses on the aetiology of multiple pathology. However, none of these have been tested. Two kinds of explanations are mentioned: causal mechanisms and bias. There are also some theories about general disease susceptibility.

Causal mechanisms

Some people may be more vulnerable to co-occurrence of diseases than others because of genetic and immunologic factors, the environment they live and work in, life events, adaptive capacities, lifestyle, behavioural risk factors or (risk associated to) social status[2]. Moreover, diseases may have a common aetiology, common predisposing characteristics, or a shared pathogenesis[3 6 38]. In this respect, the ageing process demands special attention. Although the biological ageing processes within the human body are not uniform (the biological age of organs differs), they work parallel in time and result in an increasing general vulnerability[3]. Additionally, it is hypothesised that a disease in one body system can cause an accelerated ageing, which again brings about an increased general vulnerability[11 14].

Bias

In several studies, results are presented stratified according to age[6 9-11 30 35-38]. Since the prevalence of most chronic conditions, such as cardiovascular diseases, chronic obstructive respiratory diseases and locomotor diseases rises with age, this is very important. If age is not recognised as a possible confounding factor, co-occurrence of diseases might be considered as non-coincidental when the observed associations can in fact be explained by differences between certain age groups. Similar non-coincidental identification might result from not taking the patients' sex into consideration. Of course, the decision to 'adjust' for age, sex or some other covariables depends on whether these variables are studied as potential determinants or excluded. Furthermore, some authors describe detection bias resulting from the fact that people already diagnosed with one disease, contact the health care system more frequently and more extensively. Therefore, they are more likely to be diagnosed with subsequent conditions[2 7 38]. Also, they will be more alert in recognising and/or presenting other diseases themselves[2].

Diseases susceptibility

In reviews on stress, life events and illness[21 24 27], it is concluded that while illness is related to stress and life events, individual capacities and vulnerability to stress could be crucial in this respect. Moreover, other reviews conclude that, in addition to conducting studies on the aetiology of specific diseases, it might be useful to search for factors that indicate a so-called 'disease-prone personality' or 'frailty'[22 23 31].

DISCUSSION

Co-occurrence of medical conditions is a common and increasingly frequent phenomenon with many consequences. Designs of studies on the co-occurrence of diseases vary greatly, as do their results. Because of the different choices made with regard to such aspects as the outcome measures and study population, it is difficult to compare the results. It is however clear that there is a serious health problem. Papers report on a prevalence of co-occurring diseases of less than 1%[38] to over 50%[2]. It may be associated with pain, disability and dependence for the individual. Carers and family may have to change their life styles considerably. Society too is confronted

with several economic consequences, such as the increased use of health service and a loss of productivity. Health care facilities will be confronted with more frequent contact and more complex health problems and health care situations as a result of co-occurring diseases. Because of the serious consequences, the concept should be studied extensively resulting in a better understanding.

First of all, the concept has to be unambiguous. The original definition of comorbidity assumes an additional disorder to an index disease. Other definitions are broader and diverse. We conclude that comorbidity is not a crystallised and consistent concept. This leads to indistinctness and incomparability of results, for clinicians as well as for researchers. To diminish indistinctness with regard to the terminology, we propose distinguishing between two terms:

1. comorbidity with the original definitions by Feinstein[1]: 'Any distinct additional entity that has existed or may occur during the clinical course of a patient who has the index disease under study';
2. multimorbidity defined as: 'the co-occurrence of multiple chronic or acute diseases and medical conditions within one person'.

For both definitions we further propose a classification into three categories:

a. simple comorbidity/multimorbidity; co-occurring diseases whether coincidental or not;
b. associative comorbidity/multimorbidity; not (known to be) causal;
c. causal comorbidity/multimorbidity; implying a causal relation amongst co-occurring diseases.

This classification is cumulative. All cases of multimorbidity fit into the 'simple' description, a part of those combinations show a (statistical) association, some of these indicating a causal relationship. Definitions should be classified to the highest level of association. For example, Guralnik et al[2] describe the co-occurrence of chronic diseases as well as the ratio (association) between observed and expected numbers of conditions. This should be classified as associative multimorbidity.

Secondly, attention should be paid to the choices made in multimorbidity research regarding the inclusion of patients, the type of conditions studied and the measurement used. Choices made

have consequences with respect to comparability to other studies and generalisability. For example, results may differ significantly between conditions diagnosed by a general practitioner, those diagnosed by a clinical specialist and those reported by the patient. Choices with regard to the age of people studied also greatly influence the results. Many multimorbidity studies are restricted to elderly people, probably resulting from the fact that multimorbidity is more common among the elderly. In studying causal mechanisms of multimorbidity, we consider it important to study younger multimorbid populations as well, because then results are less disturbed by the various effects of ageing, or at least the influence of age can be evaluated and accounted for.

Finally, the investigation of causes and influences and the search for populations at risk has to be intensified. Although comorbidity with one index disease has been studied extensively in clinical epidemiology research, little research has been done on multimorbidity and this research has mainly been descriptive. By studying multimorbidity, one may find patterns that indicate determinants. Knowing these patterns could be important for the development of prevention programmes. Factors such as age, sex, social class and the number of life events certainly may be significant in this respect, but explain the variance of comorbidity only to a limited extent. In future research, it is therefore important to explore other potential determinants and aetiologic factors in a broad spectrum of genetic, immunologic, psychological and social components. Also the reason why some people have less co-occurring diseases than average may teach us important lessons on the reasons why people become ill. Apart from known comorbidity of cardiovascular disease and diabetes mellitus etc. and apart from the influence of social status or the social gain of being ill, there seems to be some general susceptibility to disease that is different among individuals. Genetic, immunologic, psychosocial factors as well as earlier experience with disease and its consequences may influence the degree of susceptibility. Preferably this research should be longitudinal in order to be able to confirm causal relationships. Since general practice deals with a non-selected full morbidity spectrum in the community, primary care based studies may be expected to make a useful contribution to such research.

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CHAPTER 3

METHODOLOGY AND ANALYSIS IN COMORBIDITY AND MULTIMORBIDITY RESEARCH

Submitted as:

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Methodology and analysis in comorbidity and multimorbidity research

ABSTRACT

Study objective

To describe methodological decisions that have to be made when studying comorbidity and multimorbidity and to present appropriate analytical techniques as well as related software.

Questions

- How can comorbidity and multimorbidity be operationalized with respect to the number and type of diseases studied?
- What possible confounders and effect modifiers are important in comorbidity and multimorbidity research?
- Which outcome measures are available and how can multicomparison problems be handled?
- Which software is available for the analyses?

Main results

Choices regarding the number and type of diseases studied, result in considerable differences of the incidence and prevalence rates of comorbidity and multimorbidity found. Incidence and prevalence rates found can be largely influenced by age, sex, and other possible confounders. Additional to crude descriptive measures, comorbidity can be studied using odds ratios and relative risks. Multimorbidity can be studied using observed/expected ratios. Basic analyses of comorbidity can be performed using standard statistical packages. Two original programmes were developed for the analysis of the distribution of multimorbidity (MultiExpect) and statistically unexpected comorbidity (CombiExpect) respectively. As some analyses are subject to multicomparisons, external validity testing is recommended.

Conclusions

Analysis of comorbidity and multimorbidity has its specific problems. Some solutions for these problems as well as available software are available however.

INTRODUCTION

Although there is an increasing interest in research on multiple pathology during the last years, few papers have been published on the methodology of comorbidity and multimorbidity research. As a result, researchers in this field often have to find out by trial and error the best and most feasible ways to study and analyse multiple pathology.

This paper describes some methodological choices that have to be made, as well as the advantages and disadvantages of different analytical strategies. These strategies will be illustrated with examples using data from the Registration Network Family Practices (RNH), a large general practice based datasystem[1], and from recent studies[2] on the determinants of multimorbidity and comorbidity. The focus is on research using comorbidity or multimorbidity as the main outcome measure, but much of the reasoning may also be applicable to studies in which comorbidity or multimorbidity are used as intermediate or independent variables.

CHOICES REGARDING THE OPERATIONALIZATION OF COMORBIDITY AND MULTIMORBIDITY

Before studying determinants or consequences of multiple pathology a number of conceptual decisions have to be made.

Comorbidity or multimorbidity?

The first decision to be made is to choose between focusing on a specific disease with accompanying conditions or on co-occurring diseases in general, without any hierarchical order. In other words, studying *comorbidity* - that is 'the existence or occurrence of any distinct additional entity during the clinical course of a patient who has the index-disease under study'[3] - or studying *multimorbidity*, 'the co-occurrence of multiple chronic or acute diseases and medical conditions within one person'[4]. The central research question has to be the guide in choosing between comorbidity and multimorbidity. E.g., when studying determinants of the natural course of peripheral arterial occlusive disease (PAOD), it is most logical to measure comorbidity, because the outcome is (the index disease) PAOD, with or without its additional (comorbid) conditions. However, if the main interest is the impact of different coping styles on health, it is

more appropriate to use potential multimorbidity as outcome, as an operationalization of health status. Both comorbidity and multimorbidity can be classified in three cumulative categories[4]: simple co-/multimorbidity (the co-occurrence of diseases, whether coincidental or not); associative co-/multimorbidity (statistical association, not (known to be) causal); and causal co-/multimorbidity (implying a causal relation amongst co-occurring diseases).

Number and type of diseases

The second choice is related to the number of diseases included in the operationalization and analysis of comorbidity and multimorbidity. The number of diseases included is decisive for the amount of comorbidity or multimorbidity found. A higher number of diseases included in the calculation generally results in a higher frequency of occurrence of comorbidity or multimorbidity. E.g., the proportion of subjects in the RNH database aged 65 or older suffering from two or more disorders from a list of four (hypertension, emphysema, psoriasis and osteoporosis) was 2.8%. When glaucoma, diabetes and gout were added to this selection of diseases the prevalence of multimorbidity in the same population rised to 8.9%. When deciding how many and which diseases are included, different criteria can be used: the prevalence or incidence of diseases or the type of diseases.

The importance of abundance

Often in multimorbidity research calculations are limited to a few highly prevalent conditions[5-8]. Obviously, the use of highly prevalent diseases has statistical advantages, since co-occurrences of diseases with low prevalences are rare. Besides, it can be argued that research on highly prevalent phenomena is more relevant to society, because it affects many people. On the other hand, also a large number of people are suffering from a variety of less prevalent diseases. For example, when looking at all diagnoses concerning respiratory diseases (N=27) within the RNH database (using the ICPC classification), only 4 diseases had a prevalence higher than 1%: chronic bronchitis, COPD, asthma and hay-fever. Together they affected 10% of the population. However, an additional 3.7% of the population without any of those four conditions, were diagnosed with at least one of the other 23 less frequent respiratory diseases. Furthermore,

excluding a large number of diseases might result in a non-realistic view on the occurrence and nature of comorbidity and multimorbidity. The more limitations are used, the less representative and thus the less relevant the results can be for (part of) the population. Until now most studies that have been published concentrated on a relatively small number of diseases. Only a few studies used little limitations concerning the diseases included[2 9 10].

Which types of diseases?

Another selection criterion used is the type of disease studied. Kolnaar et al[11], for example, studied the clustering of respiratory diseases. More often clustering of psychiatric morbidity[12 13] or chronic diseases[5 8 14] is analysed. When studying the prevalence of multimorbidity this may be a sensible approach. There is little chance that two (or more) acute and short-lasting conditions will co-occur, unless one causes the other[15]. However, depending on the research subject, in comorbidity research it might be useful to include chronic as well as acute problems. Furthermore, it should be noted that applying unusual selection criteria for disorders hampers comparison of the results to other studies.

Diseases and disease entities

The main decision to be made before the start of the study is whether or not to account for known pathophysiological relationships between diseases. E.g., does diabetes mellitus, retinopathy and a diabetic foot in one person count as one or as three diseases? Again, the research question is the main guide in decision making. For example, in a study on the complications of diabetes one is probably interested in the whole spectrum of co-occurring diseases, whereas in other studies it might be more interesting to gain insight into various disease entities. An obvious difficulty when taking pathophysiological relations into account, is that only limited knowledge on those relations is available yet.

Apart from the differences regarding the number and type of diseases included, there are many other differences between studies, like restrictions regarding age groups or special care settings[4]. To estimate the differences that result from the disease definition, the approaches of three published studies on multimorbidity were reproduced, standardising all variables except the

disorders included, using data from the RNH (using data available at September 1, 1994), and including subjects aged 65 or older of both sexes. Table 1 shows the very different prevalences of multimorbidity, when using the operationalizations of previous studies by Schellevis et al[8], Guralnik et al[5] and Van den Akker et al[2] respectively.

TABLE 1: Percentage of subjects aged 65 or older in the RNH with zero, one, and two or more prevalent diseases using different selections of diseases

	no diseases	one disease	two or more diseases (multimorbidity)
	%	%	%
Schellevis et al[8]*	45.4	36.5	18.1
Guralnik et al[5]**	33.5	35.9	30.6
van den Akker et al[2]***	12.0	18.7	69.3

* Schellevis et al identified patients known with one or more of five following conditions: hypertension, diabetes mellitus, chronic ischemic heart disease (angina pectoris, previous myocardial infarction, coronary sclerosis), chronic non-specific lung disease (asthma, chronic bronchitis, emphysema), and osteoarthritis of hip and/or knee

** Guralnik et al identified patients who reported having one or more of nine following conditions: arthritis, hypertension, cataracts, heart disease, varicose veins, diabetes, cancer (except non-melanoma skin cancer), osteoporosis or hip fracture and stroke

*** Van den Akker et al identified patients known with one or more of 335 chronic and recurrent disorders

CHOICES REGARDING THE ANALYSIS OF COMORBIDITY AND MULTIMORBIDITY

As a logical consequence of the various ways in which multiple pathology is studied, a variety of analytical methods and measures to express the co-occurrence of diseases is available.

Descriptive analyses

COMORBIDITY - Descriptive analyses can be used, such as the number of diseases additional to an index disease. For example Kisely and Goldberg[16] reported comorbidity as the number of physical symptoms additional to three different psychiatric diagnoses. Also the type of additional conditions is often mentioned when reporting on comorbidity, e.g. in a study on diagnosable psychiatric disorders in new patients with ulcerative colitis[17].

MULTIMORBIDITY - Descriptive analyses for multimorbidity (focusing on co-occurring diseases without appointing an index disease) are prevalence and incidence rates, that give insight into the co-occurrence of health problems. Commonly used are the average number of conditions, or the

proportion of a population with a certain number of conditions, sometimes stratified to age and/or gender[6 14]. Some studies also describe combinations of diseases that occur frequently[6 18 19].

Observed and expected co-occurrence

COMORBIDITY - Regularly the actual co-occurrence of diseases is related to the statistically expected co-occurrence, assuming independence. In this way, associations beyond chance can be identified. In general there are two ways to do this.

First, the use of an odds ratio (OR)[20] or relative risk (RR) of diseases in patients with and without the index disease, can provide insight into the co-occurrence of two diseases. When the OR or RR has value 1.0 (or does not differ significantly from one) the combination occurs as frequently as expected. When its value is significantly greater than 1.0 the combination is judged to occur more frequently than expected, when its value is significantly below 1.0 the occurrence of one disease is negatively associated with the occurrence of the other diseases (e.g. malaria and sickle cell anaemia). When analysing comorbidity, it is more appropriate to calculate the RR, that considers one of the diseases to be the exposition, and could be interpreted as the presence (versus the absence) of the index disease. The RR changes if the other disease is considered as the exposition factor. The OR however, reflects the association between two diseases, without considering one of them as the index disease.

Secondly, the expected co-occurrence of diseases can be calculated as the product of the separate prevalences, thus assuming statistical independence of the diseases[5 8 21 19]. For example, a study on the comorbidity of psoriasis. The prevalences of psoriasis and obesity (with BMI>30) among the 18,600 subjects aged 50 years or older in the Registration Network Family Practices were 2.8% and 6.0% respectively. The expected co-occurrence thus was (0.028)(0.06)(100)=0.17% or 32 subjects. The actual (or observed) co-occurrence of psoriasis and obesity in this population was 0.15% or 27 subjects. The observed/expected ratio is 0.84, which represents that the actual co-occurrence was somewhat less than expected. The distribution of the observed and expected number of diseases might be statistically tested using a chi-square test.

MULTIMORBIDITY - Using the same principles one can estimate the probability of occurrence of a specific number of diseases, given a set of diseases. For each number of co-occurring diseases

all possible combinations have to be taken into account. E.g., a study on the co-occurrence of 4 diseases (lung cancer (LC), diabetes (DM), osteoporosis (OP), and hypertension (HT)). When calculating the expected proportion of subjects having two of those diseases, the probabilities of having LC+DM, LC+OP, LC+HT, DM+OP, DM+HT, and OP+HT have to be added. Again calculations are based on the separate prevalences of the diseases included in the study. Resulting proportions of expected and actual subjects with no, one, two etcetera co-occurring diseases can statistically be tested by means of a chi-square test or can be represented by a ratio of the observed divided by the expected. E.g., when studying 335 chronic and recurrent diseases, using data from the Registration Network of Family Practices, it is expected that 29.6% of all people will have none of those diseases, while 36.4% are expected to have exactly one disease, the other 34% are expected to have two or more diseases. However, it showed that 43.6% had no disease, 26.6% had one disease and 29.8% had two or more diseases. The expected and observed number of prevalent diseases differed significantly for all age and sex groups[2].

Another example of presenting the amount of co-occurring diseases is the probability of having at least one more disease, given the number of diseases already present[14]. This approach can also be used to analyse co-occurrences of specific diseases.

CHANCE ASSOCIATIONS - It is also possible to compare the observed and expected occurrence of specific combinations of diseases or the observed and expected pattern of all specific combinations possible. To achieve this, many calculations and large samples are needed. Screening of data sets for combinations of large numbers of diseases that have an unexpectedly high or low co-occurrence inevitably produces a number of chance findings. It is important to validate the initial explorative and hypothesis inducing findings in external populations. If this is not possible (yet), the own study population can be split non-randomly, for example following the chronology of inclusion, provided both populations are sufficiently large. When doing so, it is important that both parts are clinically similar and in this regard meet the criteria of an external population.

Confounders and effect modifiers

COMORBIDITY - An important point of concern when analysing comorbidity is the influence of effect modifying or confounding variables. For example, as age is a strong determinant of many diseases, it is always important to take this variable into consideration when analysing the co-occurrence of diseases. Part of the co-occurrence of diseases can be explained by the known influences of age (e.g., benign prostate hypertrophy and osteoarthritis). Also other variables can be very influential. If these influences are not taken into account or at least described, this can lead to unrealistic and therefore irrelevant outcomes.

When analysing combinations of two diseases, known confounders can be adjusted for using a multiple regression analysis (using one of the diseases as the dependent variable) or a stratified analysis according to Mantel-Haenszel[22]. When analysing combinations of three or more co-occurring diseases, stratified analyses are a good option as long as the study population is sufficiently large, giving the opportunity to account for the main confounders. Another option is to carry a stepwise multiple logistic regression analysis, evaluating the determinants of the presence of an additional disease conditional upon an already present disease or combination of diseases.

MULTIMORBIDITY - Because of the influence of various factors on the occurrence of diseases in general, it is also important to pay attention to confounders and effect modifiers when analysing multimorbidity. Again, age is the most obvious determinant. In multiple regression analysis with the presence or absence of multimorbidity as the dependent variable, it is fairly simple to adjust for age by including age as an independent variable. Other confounders can be handled likewise.

SOFTWARE TO ANALYSE COMORBIDITY AND MULTIMORBIDITY

Simple analysis

For the performance of descriptive analyses for comorbidity and multimorbidity any statistical package can be used. Also, selective analyses of a limited number of combinations of a few diseases can be performed making cross tabulations in standard statistical software. However, when it comes to the calculation of expected co-occurrence of larger numbers of diseases, and the statistical comparison of the observed and expected values or the adjusted RRs or ORs of many

combinations in relation to a set of determinants, no standard software is available. In order to perform those analyses, two computer programmes were developed.

Comparison of observed and expected distribution

The first programme (MultiExpect) evaluates the distribution of the number of diseases in a given population. It can process data sets including up to 500 different diseases. The output consists of the proportions of subjects that actually have zero, one, two, three, four and five or more diseases as well as the proportions that are to be expected, taking all separate prevalences into account. A chi-square test of the observed and expected proportions is provided. The analysis can theoretically be carried out for the total population, but it is strongly advised to also analyse subgroups (see the paragraph on confounders and effect modifiers).

Analysis of unexpected combinations

The second programme (CombiExpect) focuses on the occurrence of combinations of two diseases adjusted for age (in 5 categories) and sex. CombiExpect processes data sets including up to 500 different diseases. Combinations for which both the expected and observed value are below a given absolute threshold (of 25) are excluded, because inclusion yields unreliable estimates. The output provides the Mantel-Haenszel ORs (with 95% CI) of a fixed number of combinations with the highest absolute log odds ratios or the highest chi-square values.

Both programmes MultiExpect and CombiExpect use BMDP system files for input, and work on a VAX-alpha or Windows 95/NT computer. Programmes can be obtained (at cost price) by contacting the corresponding author.

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CHAPTER 4

MULTIMORBIDITY IN GENERAL PRACTICE: prevalence, incidence, and determinants of co-occurring chronic and recurrent diseases

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ABSTRACT

Increasing numbers of people are found to have two or more diseases at the same time, which is termed multimorbidity. We studied the prevalence, incidence, and determinants of multimorbidity and the statistical clustering of chronic and recurrent diseases in a general practice setting. Prevalence of multimorbidity increased with all age groups from 10% in the 0-19-year-old age group up to 78% in subjects aged 80 and over. Increasing age, lower level of education, and public health insurance were related to the occurrence of morbidity, but even more strongly to the occurrence and degree of multimorbidity. The one-year incidence of multimorbidity (the new occurrence of two or more diseases in one year) was related to increasing age, public health insurance, and the presence of prevalent diseases at baseline. Statistical clustering of diseases was stronger than expected, especially among the younger subjects.

INTRODUCTION

During the last few decades the prevalence of chronic medical conditions has risen because of increased longevity[1]. As a result of the growing proportion of elderly people in the community, the prevalence of chronic conditions is expected to rise further. Moreover, it is becoming increasingly common for patients to have two or more medical conditions at the same time. A specific combination of diseases or additional diseases beyond the index disease under study is called comorbidity, while any co-occurrence of diseases is termed multimorbidity[2]. For a patient, multimorbidity may have profound implications. The degree of physical and social disability rises with the number of patients' medical conditions[3-5]. Multimorbidity also has an impact on family and friends[1]: caring may take a lot of time and physical and emotional energy; and sometimes a considerable change in lifestyle is needed[6]. Multimorbidity often requires complex therapy and care, which demands special attention, knowledge, and skills of the medical attendants and nurses. For society, multimorbidity causes an increased need for social, medical, and health care services and a loss of productivity.

Previous studies on multimorbidity reported two or more medical conditions at the same time in 3.6%[7] to over 50%[3] of the populations under study. Comparing these studies is difficult because of the many differences in methodology, population, and number and type of diseases under study. It is clear, however, that the number of co-existing diseases in a person rises with age[1 3 7 8]. Other determinants of multimorbidity have not been studied extensively, and research on the determinants of co-occurring diseases using a broad nosological spectrum is especially rare. Most of the existing research has concentrated on studying a small number of diseases in a restricted population: for example, only elderly people or only patients admitted to hospital. Therefore, it is difficult to draw more general conclusions from these studies. Because of the serious consequences of multimorbidity for the patient, family and friends, and society, it is important to gain more insight into the occurrence and the determinants of multimorbidity.

In this article we report on the prevalence and incidence of multimorbidity in a Dutch general practice population. Multimorbidity is especially relevant in general practice; whereas most clinical specialities focus on one or more organ systems, the general practitioner (GP) encounters a much broader spectrum of medical conditions. As a result, general practice is a very appropriate

setting to study multimorbidity. In the Netherlands almost all people are registered in a general practice. General practitioners deliver continuous care to their patients, and they are the gate-keepers to the other health care facilities. After referral all medical reports are reported to them. As a result, general practitioners have comprehensive information on the health status of their patients.

The current study uses a broad nosological spectrum classified within a large number of separate medical conditions. There were no limitations regarding age, use of health care services, or presence or absence of certain diseases. In fact, since in the Netherlands all individuals are registered in a general practice, the epidemiological denominator represented the general population. The influence of basic socio-demographic characteristics on the occurrence of multimorbidity was evaluated. By gaining insight into these relations we aim to trace determinants of susceptibility to disease in general and to be able to identify vulnerable groups.

Finally, we studied the statistical clustering of diseases in our study population. The observed number of diseases within patients was compared to the statistically expected number (assuming independence) and tested for significant differences. In this study we did not focus on specific combinations of diseases, our main goal being to examine whether or not diseases cluster within persons.

METHODS

Context

This study was carried out within the context of the Registration Network Family Practices (RegistratieNet Huisartspraktijken, RNH). This is a continuous and computerised database in which 42 general practitioners, working in 15 different practices in the South of the Netherlands, are participating. All relevant health problems are registered. A health problem is defined as 'anything that has required, does or may require health-care management and has affected or could significantly affect a person's physical or emotional well-being'. Health problems are only coded by the GPs if they are permanent (no recovery expected), chronic (duration longer than 6 months), recurrent (more than 3 recurrences within 6 months), or when they have lasting consequences for the functional status or prognosis of the patient. Problems are coded according

to the International Classification of Primary Care (ICPC)[9], using the criteria of the International Classification of Health Problems in Primary Care (ICHPPC-2)[10] for diagnoses.

In addition the database contains background information on the patients' sex, date of birth, living arrangement, level of education, and type of health insurance. The registered data are continuously updated and historically cumulated for each patient. Population membership only ends by migration or death. The quality of the data is ascertained by instruction and training sessions, regional consensus groups, quality control experiments, and an automated thesaurus and automated checking for erroneous or missing entries[11]. Reliability and completeness has been shown by comparisons between the RNH's cancer data and the data of the regional Cancer Registry[12] and between the RNH's epilepsy data and the Maastricht Epilepsy Case Register[11].

For this study only active ICPC codes related to diagnostic categories were selected. A problem is considered to be active if it has the attention of the GP or the patient, as reflected by present treatment, subsequent diagnostic investigations, disease monitoring or the known progressive course of a disease[11]. ICPC-codes representing symptoms and complaints were not selected. Furthermore, for calculating the occurrence of multimorbidity a number of ICPC codes were not selected (appendix A), because they represent pregnancy and delivery without pathology, double codings, test results not leading to a diagnosis, no disease, variation of normal function, superficial injuries, and risk factors. A total of 335 different diagnostic categories was included for the analysis.

Population

All results were drawn from the data set available on September 1, 1994. Our population contained 60,857 subjects of all ages, with slightly more women (51.3%) than men (48.7%).

The study population (table 1) was comparable to the Dutch population with regard to socio-demographic variables[11]. The level of education was only registered for subjects aged 25 and older, since for younger people this characteristic changes too fast.

TABLE 1: Basic socio-demographic characteristics (N=60,857)

characteristic		%
sex	male	48.7
	female	51.3
age (in years)	0-19	22.6
	20-39	31.5
	40-59	26.3
	60-79	16.9
	≥80	2.6
living arrangement	living with family	85.1
	living alone	11.8
	home for elderly/commune	1.1
health insurance	private	32.0
	public	68.0
educational level[1]	low	40.2
	secondary	26.1
	high	7.5
	not registered (<25 years)	26.2

1 Education was not registered for people younger than 25 years, because changes are too fast

Definitions

Multimorbidity is the co-occurrence of two or more diseases within one person. To estimate the prevalence of multimorbidity, the number of patients who had two or more active health problems registered on September 1, 1994, was divided by the total number of patients in the RNH database. Estimation of the one-year incidence of multimorbidity was based on the data available for the last full year (i.e. the number of patients with two or more new diagnoses occurring in 1993 divided by the total number of patients). The basic socio-demographic characteristics used in the analyses were: sex (males and females), type of health insurance (private and public), level of education (low, secondary, high), age in five categories (0-19, 20-39, 40-59, 60-79, 80 years and older), and living arrangement in three categories (living with family, living alone, living in a home for the elderly).

Analysis

Initially, the relation between each of the socio-demographic characteristics and the occurrence of prevalent and incident multimorbidity was evaluated with a chi-square test. Additionally, the independent relation between each characteristic and the prevalence of multimorbidity was examined from the odds ratios (OR) and their 95% confidence intervals (95% CI) adjusted for the other characteristics by means of a backward stepwise logistic regression analysis. The dependent variable was the occurrence (yes/no) of prevalent multimorbidity (two or more versus one disease or none). Independent variables were sex, health insurance, living arrangement, level of education, and age group.

Logistic regression analyses were also performed with different cut-off points of the dependent variable (≥1 versus 0, 1 versus 0, 2 versus 0, ≥3 versus 0, 2 versus 1, and ≥3 versus 1 disease), in order to analyse the differences between morbidity and multimorbidity and to study whether the degree of multimorbidity (the number of co-occurring diseases) mattered. Thereafter, logistic regression analysis was performed, using the occurrence (yes/no) of incident multimorbidity as the dependent variable. The number of prevalent conditions at baseline was added as an independent variable, indicating the degree of (multi-)morbidity in the past.

The observed probability of having a specific number of diseases is more meaningful when compared to the expected probability, to test whether or not there is statistical clustering of diseases. We calculated the expected probability, with statistical independence of diseases as the null-hypothesis (i.e., the random co-occurrence of diseases)[3]. Both the observed and expected frequencies were calculated overall as well as for different age and sex categories. The method used to calculate the expected probabilities is explained in appendix B. The larger the number of conditions under study, the more complicated the executions of this computation.

Differences between observed and expected probabilities were statistically evaluated with a chi-square test. Then ratios of the observed and expected probabilities were calculated, as a measure of statistical clustering of diseases in patients. A ratio of value 1 indicates that the actual proportion of subjects with a specific number of diseases equals the expected proportion.

BMDP software was used for both crude data analysis and logistic regression analysis[13]. Special software was developed to analyse the observed and the expected distribution of diseases.

TABLE 2: Prevalence and incidence of multimorbidity (two or more co-occurring diseases), stratified for age and sex (N=60,857)

sex	age (years)	number of patients	% with prevalent multimorbidity	mean number of prevalent diseases	% with incident multimorbidity in 1993	mean number of new diseases in 1993
males	0-19	6,994	10.7	0.51	0.5	0.06
	20-39	9,317	16.0	0.68	0.6	0.06
	40-59	8,243	33.6	1.27	1.3	0.11
	60-79	4,596	60.9	2.42	3.7	0.21
	≥ 80	480	74.2	3.24	5.6	0.31
females	0-19	6,723	9.2	0.46	0.3	0.05
	20-39	9,804	18.8	0.78	0.6	0.08
	40-59	7,821	35.9	1.35	1.2	0.12
	60-79	5,739	64.9	2.61	3.2	0.21
	≥ 80	1,140	79.9	3.57	6.1	0.29
total		60,857	29.7	1.21	1.3	0.11

RESULTS

Prevalence

Overall, multimorbidity (two or more diseases at the same time) was found in 29.7% of the registered subjects. The mean number of prevalent diseases was 1.21 (95% CI 1.19-1.22) and varied from 0.46 in the youngest females to 3.57 in females aged 80 years and older, and from 0.51 in the youngest males to 3.24 in the oldest males. A higher prevalence of multimorbidity was found among the elderly (chi-square test for trend, p<.0001), among women (chi-square, p<.0001), and among subjects with a low level of education (chi-square, p<.0001) (table 2).

Furthermore, multimorbidity was more common among subjects with public health insurance compared to those with private health insurance (chi-square, p<.0001) and less common among subjects who were living with a partner or family compared to subjects living alone and those living in a home for the elderly (chi-square, p<.0001).

Logistic regression analysis using the occurrence of prevalent multimorbidity as the dependent variable showed multimorbidity to be independently related to all independent variables included

TABLE 3: Relation between socio-demographic characteristics and the prevalence of multimorbidity. Adjusted odds ratios for ≥2 vs. ≤1 condition, N=41,290

characteristic*		odds ratio	95% CI
sex	males	1.00	
	females	1.12	1.07-1.17
age (in years)	25-39	1.00	
	40-59	2.36	2.24-2.50
	60-79	7.12	6.70-7.56
	≥80	13.9	12.1-15.9
living arrangement	family	1.00	
	alone	1.05	0.99-1.11
	home for elderly	1.69	1.39-2.06
health insurance	private	1.00	
	public	1.29	1.22-1.36
educational level	low	1.00	
	secondary	0.84	0.80-0.88
	high	0.75	0.69-0.81

*None of the independent variables passed the 0.05 remove limit

TABLE 4: Relation between socio-demographic characteristics and the prevalence of (multi)morbidity, using different cut-off points.
Odds ratios (and 95% CI) resulting from logistic regression analysis

characteristic	≥1 vs. 0 (N = 41,290)	1 vs. 0 (N = 25,647)	2 vs. 0 (N = 21,216)	≥3 vs. 0 (N = 23,405)	2 vs. 1 (N = 17,885)	≥ 3 vs. 1 (N = 20,074)
sex						
females vs. males	1.11 (1.07-1.16)	1.06 (1.01-1.12)	1.12 (1.05-1.19)	1.15 (1.07-1.22)	1.07 (1.01-1.14)	1.12 (1.06-1.20)
educational level						
secondary vs. low	0.88 (0.84-0.93)	0.96 (0.91-1.02)	0.91 (0.85-0.97)	0.76 (0.70-0.81)	0.93 (0.87-1.00)	0.77 (0.71-0.83)
high vs. low	0.80 (0.74-0.86)	0.90 (0.82-0.98)	0.79 (0.70-0.89)	0.64 (0.56-0.72)	0.88 (0.78-0.99)	0.71 (0.62-0.81)
age (in years)						
40-59 vs. 25-39	1.99 (1.90-2.09)	1.50 (1.42-1.58)	2.16 (2.01-2.32)	3.99 (3.67-4.35)	1.43 (1.33-1.54)	2.64 (2.42-2.88)
60-79 vs. 25-39	5.88 (5.50-6.28)	2.53 (2.34-2.74)	5.78 (5.29-6.31)	20.7 (18.9-22.8)	2.28 (2.09-2.48)	8.16 (7.45-8.93)
≥80 vs. 25-39	10.7 (8.81-12.9)	2.67 (2.12-3.37)	8.75 (6.99-11.0)	47.3 (38.5-58.2)	3.22 (2.65-3.92)	17.3 (14.5-20.7)
living arrangement						
alone vs. family	1.06 (1.00-1.13)	1.05 (0.98-1.14)	1.05 (0.96-1.15)	1.11 (1.01-1.22)	0.99 (0.91-1.08)	1.03 (0.95-1.12)
home vs. family	1.64 (1.28-2.10)	1.30 (0.97-1.75)	1.72 (1.26-2.35)	1.98 (1.47-2.69)	1.35 (1.02-1.79)	1.62 (1.26-2.10)
insurance						
public vs. private	1.31 (1.24-1.37)	1.20 (1.13-1.27)	1.37 (1.27-1.47)	1.48 (1.37-1.60)	1.12 (1.04-1.21)	1.19 (1.10-1.28)

in the analysis, that is sex, age, type of health insurance, level of education, and living arrangement (table 3). Overall, women, elderly subjects, subjects with a low level of education, subjects with public health insurance, and subjects living in a home for the elderly were more at risk.

The same determinants were related to morbidity in general and to multimorbidity (table 4). However, age, education, and type of insurance were more strongly related to multimorbidity than to morbidity in general. In fact, the higher the number of diseases used as a cut-off, the stronger the relations.

Incidence

Most of the population (90.8%) did not develop any new diseases in 1993, while 7.9% had one new disease (table 2). The remainder (1.3%) had two or more new diseases diagnosed in 1993. On the average, the number of new diagnoses in 1993 was 0.11 per person, varying from 0.06 in young subjects (0-19 years) to 0.31 in the elderly (80 years and older).

Crude data analysis showed no differences between men and women with respect to the one-year incidence of multimorbidity. With regard to the other socio-demographic characteristics, the relations were similar to those concerning prevalence of multimorbidity. Two or more new diseases were more often found among older than younger subjects (chi-square test for trend, $p<.0001$), among subjects with a low level of education (chi-square test for trend, $p<.0001$), among subjects with public compared to private health insurance ($p<.0001$), and among subjects living alone and those living in a home for the elderly, compared to those living with family (chi-square test, $p<.0001$).

Logistic regression analysis using the occurrence of incident multimorbidity as the dependent variable (two or more new diseases versus none or only one new disease in 1993) showed the elderly as well as subjects with public health insurance to be at higher risk (table 5). Level of education, sex, and type of living arrangement did not show an independent relation with the one-year incidence and were successively removed from the statistical model. Furthermore, the presence of prevalent diseases at the start of the incidence period influenced the risk of

developing multiple disease in the next year; subjects who already had two or more diseases were at higher risk of getting two or more new diseases than subjects who had no disease.

TABLE 5: Relation between socio-demographic characteristics* and the one-year incidence of multimorbidity. Adjusted odds ratios for ≥2 vs. ≤1 new condition, N=41,290

characteristic		odds ratio	95% CI
age (in years)	25-39	1.00	
	40-59	1.79	1.39-2.31
	60-79	4.38	3.43-5.59
	≥80	7.84	5.75-10.7
health insurance	private	1.00	
	public	1.34	1.12-1.60
number of prevalent diseases at January 1, 1993	none	1.00	
	one	1.06	0.84-1.34
	two	1.38	1.12-1.69

* Education, sex, and living arrangement were successively rejected during the stepwise model building

Observed and expected number of diseases

Overall, the ratio of the observed and the expected number of diseases had a U-shaped distribution. More patients than expected did not have any disease. Also more often than expected, patients had four or more diseases. This was found in both men and women.

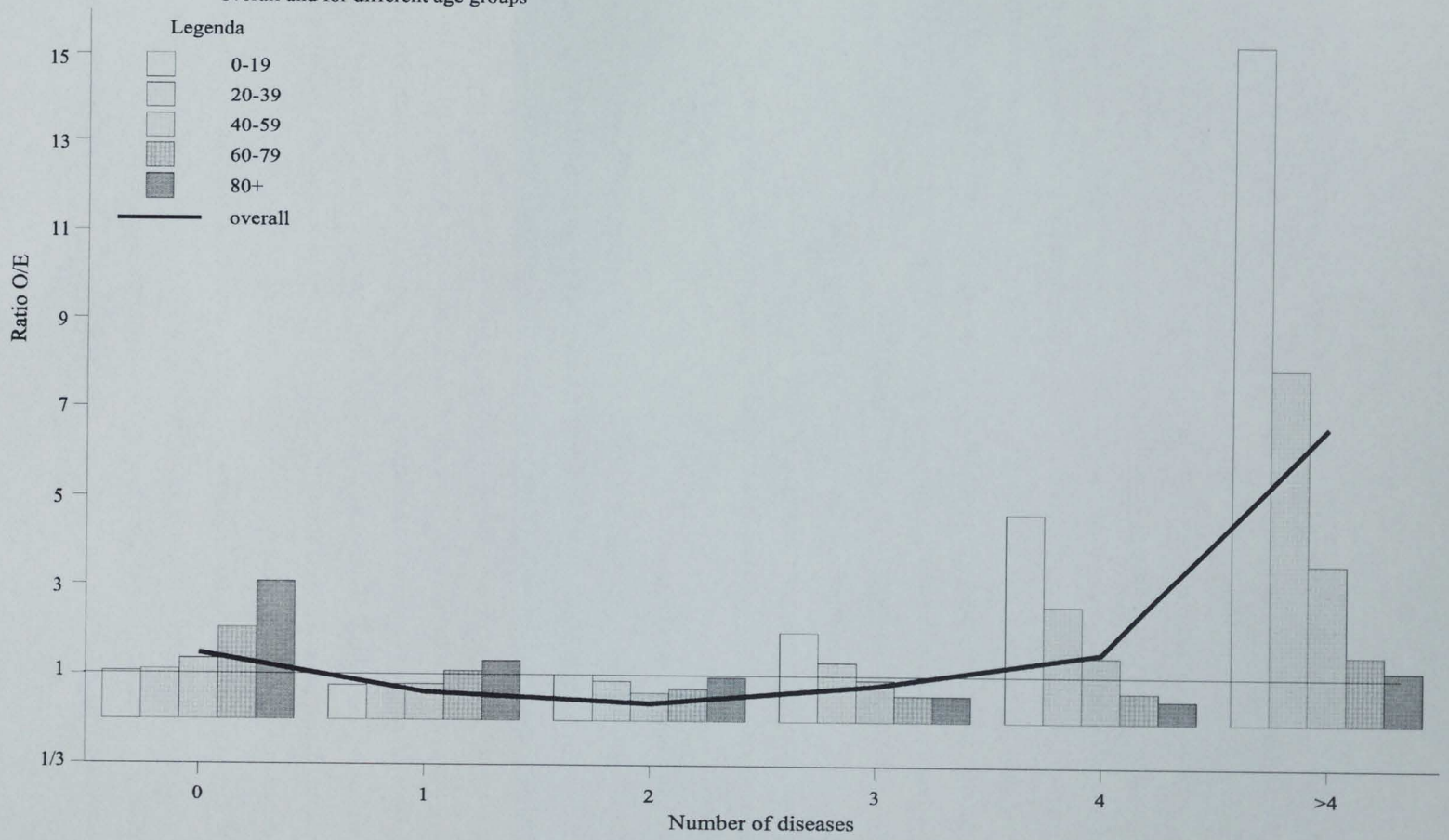
Among younger subjects, the distribution of diseases was broadly as expected for zero, one and two diseases. Three or more diseases was much more common than expected. In the older age groups on the other hand, more subjects than expected had no disease or only one disease. Four or more diseases occurred somewhat more frequently than expected (see figure 1).

The differences between the observed and expected number of diseases were strongly statistically significant ($p<.0001$) for both sexes and all ages.

DISCUSSION

Our analyses showed that multimorbidity - the co-occurrence of two or more chronic or recurrent diseases within one person - is a common phenomenon with a prevalence of 29.7% in our study

FIGURE 1: ratios of observed and expected (co-)occurrence of diseases, overall and for different age groups



population, ranging from 10% in the 0-19-year-old age group to 78% in subjects aged 80 and older. Most other studies have reported lower prevalences[3 4 7 14], which can be explained by the limited number of conditions included in those studies. Parkerson et al[15] is the only one who found a higher overall prevalence of multimorbidity (52.4%). The setting of his research was comparable to ours, but patients included those visiting the family medical centre during the study period, while our data concerned all patients registered in general practice, including those who had not visited their GP recently. Our results are comparable to those of Newacheck et al[5], who studied the prevalence of chronic conditions among adolescents. Van Weel[16] also reported similar prevalences of multimorbidity in a population of 65 years and older, despite the fact that his study focused on the top 10 chronic diseases. Apparently, the greater part of multimorbidity is accounted for by a relatively small number of diagnoses.

Only one other study concerning the incidence of multiple diseases was found. Meyboom-de Jong[17] reported two or more new chronic conditions in one year in 19% of a population of patients aged 65 years and over. This is considerably more than we found: overall 1.3%, 3.4% in 60-79-year-olds, and 6.0% in subjects of 80 years and older. However, Meyboom-de Jong also included only patients visiting the GP.

An important part of the variations among the studies is because of the selection of number and type of conditions under study. In our study we used data from the RNH; chronic, recurrent, and permanent conditions and conditions with lasting consequences. This resulted in a study with a large number of different medical conditions. A different scope, for example entering all disorders presented to the GP (e.g., including a single episode of common cold) or the number of medical conditions as reported by patients, would have produced different figures. The more exhaustive the method of detecting diseases (e.g., all chronic and acute diseases versus only chronic or permanent diseases), the higher will be the number of observed diseases and the higher the prevalence of multimorbidity.

Determinants of morbidity in general have been studied extensively. Generally, a higher risk is reported for elderly subjects and for subjects with a low socio-economic status. Most studies on multimorbidity only have taken age into consideration, sometimes together with sex. Many of these studies reported an increased risk with rising age[3 7 18]. Guralnik et al[3] also reported a

higher prevalence of multimorbidity among women. In our study we found increasing age, a lower level of education and public health insurance to be related to the likelihood of having two or more diseases at the same time. The one-year incidence of multimorbidity was related to age, type of health insurance (with a higher risk for patients with a public health insurance), and the number of diseases at the start of the incidence period. We found no evidence for sex to be strongly related to either prevalence or incidence of multimorbidity, when adjusting for other socio-demographic characteristics. Multimorbidity and morbidity generally had similar determinants. However, age, level of education, and type of health insurance were even more related to multimorbidity than to morbidity in general and therefore can be considered to be independent determinants of multimorbidity. No other studies on this subject were found.

The relation between the number of diseases and the ratio of the observed and expected occurrence was U-shaped. This U-shape, more or less pronounced, was seen in both males and females and in the different age groups, although flattened with rising age. The finding of this U-shape indicates rejection of our null-hypothesis stating that diseases have a random distribution. In younger subjects the co-occurrence of three or more medical conditions was far more frequent than expected. This may be because most young subjects either are very healthy or have serious medical conditions, with co-existing (related) medical conditions. Perhaps young subjects with many co-occurring diseases are less likely to survive into old age. This might explain the flattening of the U-shape as subjects get older. However, Guralnik et al[3] also found a U-shaped distribution of the observed and expected number of diseases in a population of subjects aged 60 years and older.

The flattening of the curve might indicate that multimorbidity is not only far less prevalent but also far less expected among younger people than among older people. Among the elderly (60 years and older) the greater part of prevalent multimorbidity can be explained from the rising prevalence of chronic conditions and the coincidental co-occurrence of these conditions.

Another explanation of the U-shaped distribution might be detection bias: once people are diagnosed with one disease they might contact the health care system more frequently than other people; they are examined more frequently and extensively. Therefore, they are more likely to

be diagnosed with subsequent conditions[3] [7]. As a result the registration might show a disproportionate number of people with no disease or multiple disease.

The distribution and co-occurrence of diseases can be arranged in terms of a previously used classification of comorbidity[19]. Schellevis[19] made a distinction between concurrent comorbidity, indicating the co-existence of diseases without a satisfying explanation; cluster comorbidity, describing a distribution of diseases that is significantly different from the distribution by chance; causal comorbidity, where there is a proven pathophysiological relation between diseases; and complicating comorbidity, where the existence of one disease is obligatory for the occurrence of another disease. In a previous review of the literature[2] we suggested a related classification for comorbidity and multimorbidity following a scale of increasing association, distinguishing simple comorbidity/multimorbidity describing any co-occurrence of diseases, associated comorbidity/ multimorbidity noticing a statistical association not (known to be) causal, and causal comorbidity/ multimorbidity implying a causal relationship among co-occurring diseases. Applied to this study this means we have found associated multimorbidity; the distribution of diseases in our population shows concentrations in subgroups that differ significantly from the distribution by chance. Part of the associations might be causally related.

In this study we have counted all active diagnostic codes. Obviously, studying specific combinations of medical conditions would have resulted in tracing patterns of pathologically related diseases, like diabetes mellitus, vascular disorders, and a diabetic foot. It would be useful and interesting to develop methods to adjust for these known dependencies between diseases (i.e., causal and complicating multimorbidity) when calculating the expected co-occurrence. It is meaningful to explore remaining (concurrent) combinations of diseases that may not yet be known to be pathologically related. Unfortunately, this is not an easy task. Even the co-occurrence of diseases that are known to be pathophysiologically related, will not always be explained by this causal relation. It is difficult to develop methods to quantify to what amount a pathophysiological relation can account for the co-occurrence of two or more diseases. In future research more advanced methods are needed to analyse clustering of large numbers of diseases, adjusting for known confounders such as age and sex.

Research generally requires simplification of reality. The point is to make enough limitations to be able to process the data and, at the same time, to keep the number of restrictions limited, so that results can still be generalised. In this regard, the RNH database is very suitable because it can be assumed that the subjects included are representative for the general population in the same area[11]. There is no preselection with regard to age, level of education, and other socio-demographic features. In addition, a large number of medical conditions with a broad nosological spectrum is registered in the RNH. In registration of health problems in general practice, however, some health problems will be missing because the patient never presented them to the GP; others will not be recorded on the problem list because the GP does not judge them to be clinically relevant. Also the GP will record health problems that are asymptomatic, found by screening, chance or a diagnostic workup. The total number of conditions that are registered in the RNH thus reflects the GP's image of the health status and relevant health problems of his patients. We were not able to determine the magnitude of non-registered but perceived health problems and registrations of asymptomatic patients, because the RNH is an iatrotropic register, indicating that the problem list will be focused on symptomatic diseases and conditions that require attention and/or therapeutic interventions or medical treatment. This study was not based on a population survey. In case of increased active screening the number of medical diagnoses is expected to rise, including a number of presymptomatic conditions and risk factors. Such an augmentation, however, would not necessarily bring about an increased burden of disease and may change the impact of multimorbidity.

Furthermore, it is recommended that research into determinants and mechanisms of multimorbidity is intensified, in order to develop preventive interventions in the long term and to support the development of interventions to reduce the associated burden of illness. Attention should be paid to psychosocial as well as immunological and genetical determinants of multimorbidity. This may also provide insight into determinants of a more general disease susceptibility.

Considering the large number of patients having multimorbidity at present, and the expected increase in the future (based on predictions of the future age structure of the population), further

research into consequences of multimorbidity is important. This should not be restricted to consequences for the patients, but should include consequences in terms of the use of health care services and workload for health care workers. The results may reveal useful information for health policy makers.

In the study of multimorbidity, age should be taken into consideration as a confounder, because of the strong relation between age and the prevalence of many diseases. We advise that research into multimorbidity should not be restricted to the elderly, who are especially at risk. Also among younger adults, multimorbidity is far too common and has too much impact to be neglected.

We conclude that multimorbidity, although it increases with age, is a frequent phenomenon among all ages. Therefore, the thesis 'the clinical rule to reduce all signs and symptoms to a single diagnosis does not hold out for gerontology'[20] is not exclusively true for gerontology.

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APPENDIX A:
ICPC codes not selected for the study

all symptom and complaint codes

W78	pregnancy confirmed
W79	unwanted pregnancy confirmed
W83	abortus provocatus
W84	high-risk pregnancy
W90	normal delivery of liveborn(s)
W91	normal delivery of deadborn(s)
W92	forced of labour of liveborn(s)
W93	forced of labour of deadborn(s)
A82	late effects of trauma
A89	late effects of prosthetic device
A91	investigation with abnormal results
B85	abnormal blood chemistry
U98	abnormal urine test findings
X86	abnormality of cervical smear
A97	absence of disease
F75	contusion of an eye
F91	refractive error
F95	strabismus
H78	superficial injury of an ear
H81	excessive cerumen
H84	presbyacusis
K96	haemorrhoids
S82	birth-mark
T78	persistent duct thyroglossal, cyst
D82	caries of teeth
T83	overweight (BMI < 30 ≠ obesity)

APPENDIX B:

The calculation of the probability of the number of co-occurring diseases is based on the assumption of statistical independence of the diseases concerned.

Assume a study on the (co-)occurrence of arthritis (prevalence 31.3%), cancer (prevalence 5.4%), and diabetes mellitus (prevalence 12.5%) among women aged 80 and older (these data are derived from the RNH). What is the probability for an 80-year-old woman of having none of these, of having only one of these, of having two of these, or of having all three conditions, assuming statistical independence between the diseases? In this case one can calculate four probabilities:

- the probability of having none of those diseases;
- the probability of only one of those diseases, irrespective as to whether the patient has arthritis (AR), cancer (CA), or diabetes mellitus (DM);
- the probability of having two (out of three) diseases, irrespective as to which combination: this may be either AR and CA, AR and DM, or DM and CA;
- the probability of having all three diseases under study.

Evidently these four probabilities have to add up to 1.0.

The probability of having all three diseases is calculated as the product of the separate prevalences:

$P(3) = (p_{AR})(p_{CA})(p_{DM})$,
with p_{XX} being the prevalence of a disease
$= (0.313)(0.054)(0.125)=0.002.$

The probability of having no disease, that is neither AR, nor CA, nor DM, can be calculated as the product of all non-prevalences:

$P(0) = (1-p_{AR})(1-p_{CA})(1-p_{DM})$
$= (1-0.313)(1-0.054)(1-0.125)=0.569.$

To calculate the probability of having one disease, the probabilities of

- having AR, but not CA or DM,
- having CA, but not AR or DM,
- having DM, but not AR or CA

are summed:

$P(1) = \{(p_{AR})(1-p_{CA})(1-p_{DM})\} + \{(p_{CA})(1-p_{AR})(1-p_{DM})\} + \{(p_{DM})(1-p_{AR})(1-p_{CA})\}$
$= \{(0.313)(1-0.054)(1-0.125)\} + \{(0.054)(1-0.313)(1-0.125)\} + \{(0.125)(1-0.313)(1-0.054)\}$
$= 0.37.$

Alternatively:

$P(1) = \{P(0)*(p_{AR}/1-p_{AR})\} + \{P(0)*(p_{CA}/1-p_{CA})\} + \{P(0)*(p_{DM}/1-p_{DM})\}$
$= 0.569\{0.313/(1-0.313)\} + 0.569\{0.054/(1-0.054)\} + 0.569\{0.125/(1-0.125)\}$
$= 0.37.$

The probability of having two diseases is then calculated as:

$P(2) = \{(p_{AR})(p_{CA})(1-p_{DM})\} + \{(p_{AR})(p_{DM})(1-p_{CA})\} + \{(p_{CA})(p_{DM})(1-p_{AR})\}$
$= \{(0.313)(0.054)(1-0.125)\} + \{(0.313)(0.125)(1-0.054)\} + \{(0.054)(0.125)(1-0.313)\} = 0.06.$

These probabilities can be formulated in more general mathematical terms, which are also applicable to calculations with larger numbers of diseases:

$P(0) = \prod_i(1-p_i)$,
with p_i being the prevalence rate of disease i.

$P(1) = \sum_i P(0)*p_i/(1-p_i)$ ▲

$P(2) = \sum_i\sum_{j>i} P(0)*\{p_i/(1-p_i)\}*\{p_j/(1-p_j)\}$,
and so on for all numbers of diseases.

▲ The probability of having exactly one disease is calculated as the sum of the probabilities of having each specific disease and not having any of the other diseases. Mathematically this can be shortened to the sum of the probability of having no disease times the probability of a specific disease (divided by its complement ($1-p_i$), which is already in the P(0) formula).

$P(p_1) = p_1(1-p_2)(1-p_3)....$
$= P(0)*\{p_1/(1-p_1)\}$

CHAPTER 5

MARGINAL IMPACT OF PSYCHO-SOCIAL FACTORS ON MULTIMORBIDITY:

results of an explorative nested case-control study

Submitted as:

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Marginal impact of psycho-social factors on multimorbidity: results of an explorative nested case-control study.

ABSTRACT

This study examines differences between subjects with zero, one or two or more new diseases in a period of three years, with regard to demographic characteristics, socio-economic status, life style, medical family history and current diseases in the family, psychological and sociological characteristics. This was studied using a primary care based nested case-control study. Data were available from 3,745 cases and controls, all aged 20 years and older. All subjects were sampled from the Registration Network Family Practices, which is a computerised continuous primary care database. Cases were defined as subjects with new multimorbidity (two or more new diseases) registered in a period of three years and two groups of controls were operationalized as subjects with one or no new diseases registered in the same period respectively. Determinants were assessed by means of a postal questionnaire. Increasing age, higher number of previous diseases and low socio-economic status were strongly associated with both morbidity and multimorbidity. After adjustment for these basic variables, the occurrence of multimorbidity was more frequent among subjects who did not report (volunteer) work or study, who had an active coping style, a high occupational class and an external locus of control. Profiles for subjects at risk for morbidity and multimorbidity seem to differ.

INTRODUCTION

In clinical practice as well as in epidemiological research there is an increasing interest in multimorbidity - the co-occurrence of various medical conditions within one person[1 2] and comorbidity - the occurrence of diseases additional to an index disease[3]. In the general population there is an unequal distribution of illness among persons. Some patients rarely suffer from diseases, others are diseased every now and then, and some are burdened by (multiple) chronic diseases. Among all ages there is a high prevalence of multimorbidity. In a previous study in a general practice population, using a broad nosological spectrum, we found 10% multimorbidity among subjects aged 0-19 years old, increasing to 78% in the oldest group (80 years and older)[4]. Because of the expected ageing of Western populations[5] the overall number of people suffering from multiple disease is expected to rise further. Furthermore, an increase of the prevalence can be expected due to increasing medical knowledge and development of new medical technologies, that contribute to a prolonged survival of the chronically diseased. This phenomenon was reported by Van Weel[6], who found a rather stable incidence of the top ten of chronic diseases during the last decades, but an increase in its prevalence, particularly among subjects aged 65 and older. Especially in primary care, where the general practitioner (GP) provides continuous care, with regular contacts and patient monitoring, this will lead to more complex health care situations. Also for patients, family and close friends and society consequences will be marked.

Until now research has mainly been focused on the occurrence and consequences of multimorbidity[1 7 8]. Aetiological research has mainly been disease specific. There is an ongoing debate as to whether this is sufficient or whether there is an urgent need for a more general approach. For example, Syme[9] evaluated 50 years of epidemiologic research in the area of coronary heart disease, one of the most successful areas of disease specific aetiologic research. He concluded that together the disease specific aetiologies explain only about 40% of the occurrence, leaving 60% unaccounted for. Already in 1976 Cassel[10] stated that there is a remarkably similar set of risk factors that is related to very diverse disease entities, implying the usefulness of factor specific research additional to disease specific research. Although little is known about the mechanisms, several - mainly psycho-social - factors have been suggested to be

related to general disease susceptibility. Also Syme[11] suggested there might be factors like life changes associated with social and cultural mobility, stressful life events, and coping styles, that cause an increased disease susceptibility, with a wide range of disease outcomes. In reviews on disease prone personalities, both Thomas[12] and Friedman and Booth-Kewley [13] concluded that studies regarding disease proneness should include psychological characteristics. The evidence from research in this area, however, is scarce. Therefore, studies in this field are deemed to be explorative.

Many studies have shown the association between socio-economic status and general health, morbidity and mortality[14-18]. Furthermore, much attention has been paid to the relationship between (chronic) stress and life events on the one hand and health on the other hand[12 13 19], and to the influence of social network and social integration on health and mortality[20 21].

To identify high-risk groups in the short term and to enable the development of preventive interventions in the long term, it is important to gain insight into factors that are related to multimorbidity. Because no studies on determinants of multimorbidity are available yet, possible determinants for multimorbidity were derived from determinants of health in general. Of course disease susceptibility can also result from other than psycho-social factors, like genetic predisposition or disorders of the immune system. Selection of the factors studied was based on a review of the literature as well as on contacts with experts in the field. Because of feasibility-reasons, choices had to be made regarding inclusion and exclusion of topics. Those topics that the research group thought to be most plausible and promising were included.

In this paper we report on a nested case-control study that evaluated the relation between demographic, psycho-social, and life-style characteristics and the occurrence of morbidity and multimorbidity. The aim of this study was twofold: the exploration of the above mentioned characteristics, in order to deduce hypotheses, and the evaluation of the similarities and differences of characteristics related to either morbidity or multimorbidity.

The main research question was: Are there differences between subjects who had new

multimorbidity, new monomorbidity and no new morbidity with respect to demographic characteristics, socio-economic status, life style, personal medical history, family history, psychological and sociological characteristics?

METHODS

Background and context

This study has been carried out within the context of the Registration Network Family Practices (RegistratieNet Huisartspraktijken, RNH). This is a continuous and computerised database in which - at the time of this study - 42 general practitioners, working in 15 different practices in the South of the Netherlands, were participating. All health problems are registered on the so-called problem list. A health problem is defined as 'anything that has required, does or may require health-care management and has affected or could significantly affect a person's physical or emotional well-being'. Health problems are only coded by the GPs if they are permanent (no recovery expected), chronic (duration longer than 6 months) or recurrent (more than 3 recurrences within 6 months) or have serious or lasting consequences for the patient. Problems are coded following the International Classification of Primary Care (ICPC)[22] and using the criteria of the International Classification of Health Problems in Primary Care (ICHPPC-2) for diagnoses[23]. Thus, the relevant health problems are mostly chronic diseases. In the context of this paper these health problems are considered as morbidity. In addition the database contains background information on sex, date of birth, living arrangement (living as a family, living alone), level of education (low, secondary, high), and type of health insurance (either private of public) of the patients. The registered data are continuously updated and historically cumulated for each patient. Population membership only ends by migration or death. The quality of the data is ascertained by instruction and training sessions, regional consensus groups, quality control experiments and special software programs, such as an automated thesaurus and automated checking for erroneous or missing entries[24]. Reliability and completeness have been shown by comparisons between the RNH's cancer data and the data of the regional Cancer Registry[25] and between the RNH's epilepsy data and the Maastricht Epilepsy Case Register[26].

In the Netherlands almost all people are registered in a general practice. General practitioners

deliver continuous care to the patients, and they are the gate-keepers to the other health care facilities. After referral all medical results are reported to them. As a result, general practitioners have comprehensive information on the health status of their patients, and the population registered in the RNH is representative for the local general population.

Sample

In this case-control study cases were defined as subjects who had new multimorbidity, i.e. two or more new disorders registered on the problem list within a selection period of three years (September 1, 1992 - August 31, 1995). Controls were defined as subjects who had no new disease in this selection period of three years. Furthermore, an additional control group with one new disease registered during the selection period was sampled. Admission of this group enabled us to distinguish between factors that were related to morbidity and those that were specifically related to multimorbidity. Because of the expected small number of elderly among the controls, a group of controls aged 60 years and older was added (N=500). This operationalization of cases and controls with multimorbidity was comparable to previous research by others[7]. A total of 335 diagnostic categories [4], covering a broad nosological spectrum, were used for the selection of cases and controls. The number of diseases prevalent at the start of the selection period was not used as a selection criterion, but was taken into account during analysis.

A total of 2,500 cases and 4,250 controls all aged 20 years or older were randomly selected from the eleven participating practices of the RNH. Of the original sample 125 subjects (46 cases and 73 controls) could not be located. Furthermore before mailing the questionnaire, 512 subjects (258 cases and 254 controls) were excluded by their GP because they were illiterate, spoke little or no Dutch, or were presumed to be incapable to participate because of their mental or physical status. All other subjects (N=6,113) received a postal questionnaire, with a numerical code corresponding to the subject's code used in the RNH. Those who had not responded within three weeks received a reminder.

Questionnaire

The questionnaire was similar for cases and controls and covered socio-demographic, life style,

psychological, sociological and medical variables.

SOCIO-DEMOGRAPHIC VARIABLES contained the place of birth of the respondent and of his/her parents, religion (any, no), living arrangements (living as a family, living alone), recent changes in living arrangement, number of brothers and sisters, number of children, and current occupational status (paid job, volunteer, scholar, unemployed, retired etc.).

SOCIO-ECONOMIC STATUS (SES) is classically operationalized as three separate but linked dimensions; level of education, occupation, and income[27 28]. Social measures such as occupational class and education are related, but theoretically distinct[29]. In agreement with previous studies, the subjects' educational level and type of health insurance (which is a global indicator of income) that were available from the RNH, were used as an indicator for socio-economic status.

OCCUPATION. Subjects' current or last occupation was coded[30] and classified using a reconstruction of the EGP[31] coding scheme, which classifies occupations in five categories, based on occupational sector and required training; lower blue collar, upper blue collar, lower white collar, upper white collar, and others (students, housewives etc.). Furthermore, the current occupational status was questioned. In the analyses this was dichotomised: subjects who reported (paid or volunteer) work or school/study less than eight hours and subjects who reported eight hours or more a week.

GENERAL HEALTH INFORMATION contained information regarding height and weight, which was combined in the body mass index (BMI), where a BMI of 27 and higher was considered as cut-off for overweight[32].

HEALTH RELATED BEHAVIOUR concerned smoking, alcohol intake, and sports. To establish the smoking status, subjects were asked if they smoked currently or if they ever smoked in the past, how many cigars, cigarettes or pipes they smoked a day, how many years they smoked and when (if ever) they stopped. Alcohol intake was operationalized as current intake. Problematic alcohol intake was operationalized as 21 units or more a week for men and 14 units or more a week for women, according to the levels of safe drinking by the Royal College of General Practitioners[33]. Concerning sports, subjects were asked whether they spent any time on sports, and if they did so, which type of sport and how many hours a week.

MEDICAL FAMILY HISTORY. Subjects were asked whether their parents were alive, if not at what

age they died and from what cause. It was also registered whether grandparents, brothers or sisters died from cancer, from cardiovascular disease or from a violent cause and if they suffered from cardiovascular disease or cancer before the age of 60. Besides, the presence of chronic illness or handicap in family members of the respondent was questioned.

LONG-TERM DIFFICULTIES were measured as an indicator for chronic stress[34] using the Long-term Difficulties Questionnaire[35] with a 4-point Likert scale ranging from 'no problems' to 'severe problems'. This list aims to measure long-term difficulties, especially chronic stress related to problems with housing, work, school, finances, relationship with parents, etc. If a difficulty was relevant, subjects were asked to describe it. In agreement with previous research we added a question about difficulties concerning leisure activities[36]. Long-term difficulties that resulted from health problems were not counted in the analysis, because of interference with the outcome measure. For the analyses responders were classified as having no or one and two or more long-term difficulties.

LIFE EVENTS are defined as changes in daily life with an impact on someone's life, e.g. delivery of a child or retirement. An event is meaningful when it causes the subject harm, when important individual goals are threatened or facilitated, or when the subject's self image is influenced either positively or negatively. The list used in our questionnaire was based on the VRMG (Questionnaire Recent Events; Vragenlijst Recent Meegemaakte Gebeurtenissen)[37]. In consultation with experts the list was shortened. Subjects could score up to seven positive life events, twenty-one negative life events, and eight life events of undetermined significance. For each type of life events we defined a dichotomous score, indicating whether or not responders had had at least one event of this type in the two years previous to case selection.

HEALTH LOCUS OF CONTROL (HLOC) reflects expectancies regarding the controllability of someone's own health. The HLoC was measured using the validated Dutch version[38] of the Multidimensional Health Locus of Control by Wallston et al[39]. The HLoC has three dimensions; the Internal Locus (measuring the amount to which an individual experiences that health can be influenced by himself or herself), the Powerful Others Locus (measuring the amount to which a subject feels that health depends on powerful others, e.g. physicians) and the Chance Locus (the amount to which an individual beliefs that health is a result of chance and luck, and that it cannot

be influenced by him or herself or others). Each dimension has six items, to be answered on a 6-point Likert scale ranging from 'absolutely disagree' to 'absolutely agree'. In our study population we found a good internal consistency for the internal, external and chance locus (Cronbach's α respectively 0.74, 0.81 and 0.67). For the analyses locus scores were dichotomised, based on the contents and distribution of the scores.

COPING STYLE. Coping can be described as stress management or the adaptive reaction, thoughts and actions that are used to stand up to a stressor[40]. The short coping list (15 items) we used was based on the original 47-item 'Utrecht Coping List' (UCL)[41 42]. From this list four coping styles can be distinguished: 'active', 'social support seeking', 'avoiding', and 'palliative'[43]. Each item was answered using a 4-point Likert scale ranging from 'seldom/never' to 'very often'. The internal consistencies found for avoiding, active, palliative and seeking social support styles were 0.64, 0.84, 0.44 and 0.82 respectively. For each coping style a dichotomous score was calculated, based on the contents and distribution of the scores.

SOCIAL NETWORK represents the web of social relationships that every person maintains, including both intimate relations with family and close friends and more formal relationships with other individuals and groups[20]. It is increasingly recognised as a factor in health maintenance and survival[44-46]. Based on questions regarding living arrangement, work and study activities, sports and leisure activities subjects could participate in a maximum of nine.

VALUES are concepts or beliefs that pertain to desirable end states or behaviours, transcend specific situations, guide selection or evaluation of behaviour and events and are ordered by relative importance[47]. Schwartz mentions 10 distinct motivational types of values that were each represented by one question: selfdirection, stimulation, hedonism, achievement, power, security, conformity, tradition, benevolence, and universalism[47]. It may be hypothesised that subjects with inconsistencies in their value system (that is subjects who rate contradictory values equally important) will be inclined to experience more negative feelings, and therefore might be more susceptible to disease. It was also expected that the appraisal of certain values may be related to an increased or decreased occurrence of disease-labelling and disease presentation. Each value was scored on a 6-point Likert scale ranging from 'opposed to my principles' through 'not important' to 'very important'. In the multivariable analyses three categories were used: 'not/little

important', 'quite/very important', and 'against principles'.

Analysis

Questionnaires of all responders were pre-coded, entered on computer and verified. Raw data were extensively screened for inconsistencies using frequencies and cross tabulations.

All questionnaires had a unique personal code corresponding with the personal codes used in the Registration Network Family Practices (RNH). Problem list data from the RNH were combined with data from the questionnaire using these anonymous personal codes.

All analyses were performed for the evaluation of the determinants of morbidity and the evaluation of the determinants of multimorbidity. The 'morbidity-analysis', compared all responders with new morbidity with responders that had no new morbidity during the selection period (≥1 vs 0). The 'multimorbidity-analysis', compared responders with new multimorbidity with responders with new monomorbidity in the selection period (≥2 vs. 1). These analyses were performed to assess potential additional effects on the occurrence of multimorbidity as compared to the occurrence of morbidity in general. Three kinds of analyses were performed for both comparisons:

1. First, multiple logistic regression analysis was performed to evaluate the effects of the basic patient characteristics available from the Registration Network Family Practices (RNH) on the occurrence of morbidity and multimorbidity.
2. Second, all other possible determinants were evaluated in separate analyses, calculating odds ratios (ORs), crude as well as adjusted for the basic patient characteristics (age, sex, educational level, type of health insurance and number of prevalent conditions at the start of the study). To calculate the ORs, multiple logistic regression analyses were used, with morbidity and multimorbidity respectively serving as the dependent variable and one possible determinant (and the basic patient characteristics) entered in the model, serving as the independent variables (enter and remove limits 0.05). The value systems were analysed using MANOVA, contrasting the conflicting and compatible values.
3. Finally, all possible determinants were evaluated simultaneously in a backward stepwise

logistic regression model, separately for morbidity and multimorbidity. For the combined models the enter and remove limits were 0.10, because of the explorative nature of this study. To rule out the possibility that the results were highly depending on a rather homogenous group of subjects with a similar disease, the analyses of the combined models were repeated, excluding all subjects who were diagnosed with diabetes mellitus.

Analyses were performed using BMDP software, MANOVA was calculated using SPSS for Windows.

Handling of missing data

Apart from the subjects who did not return the questionnaire and those who returned it with (almost) all answers failing, there was a substantial number of subjects who had omitted a number of questions. For some parts of the questionnaire directives to handle limited numbers of missing items were available and applied. After these procedures still up to 9% of the items were missing for different parts of the questionnaire. Without further correction, performing multivariable analyses where a number of independent variables were combined, this would have resulted in complete data in just over 60% of the responders. Therefore, extra dummy variables were defined for the item non-response. The results were checked by repeating the model without the extra dummy variables forcing all variables that showed a significant association in the previous analysis into the model, and comparing the strength of the associations of the models with and without the extra dummy variables. In the discussion section implications of this procedure are discussed.

The study protocol was approved by the Medical Ethical Committee of the Maastricht University Hospital (azM).

RESULTS

Response

Of the 6,113 subjects that received a postal questionnaire (and a reminder) 3,745 (61.3%) subjects completed and returned the questionnaire. This was true for 1,623 controls without any new

disease in the selection period, 754 controls with one new disease in the selection period and 1,368 cases with new multimorbidity. Response was not significantly different for the case and control groups (p>.05). The responders resembled the initial sample quite well with regard to sex and type of health insurance. Subjects aged 20-29 years or those aged 80 and older were somewhat underrepresented among the responders compared with non-responders (10.4% vs. 14.3% for the 20-29 year olds, and 4.7% vs. 7.4% for subjects aged 80 and older). Compared to non-responders, responders somewhat more often lived together with a partner or family (OR = 1.35 (1.16-1.56)) and had a higher level of education (secondary vs. low OR = 1.41 (1.24-1.60);

TABLE 1: Relations between morbidity (≥1 vs. 0), multimorbidity (≥2 vs. 1) and basic patient characteristics (sex, age, level of education, type of health insurance and number of prevalent diseases at the start of the study). Reported are ORs and 95% CIs, N = 3,742

	N	morbidity	multimorbidity
age (in years)			
20-29	390	1.00 (reference)	1.00 (reference)
30-39	636	1.04 (0.81-1.35)	1.18 (0.81-1.72)
40-49	685	**1.43** (1.11-1.86)	1.11 (0.78-1.60)
50-59	544	**1.55** (1.18-2.04)	**1.52** (1.03-2.24)
60-69	750	1.22 (0.94-1.58)	**1.95** (1.33-2.85)
70-79	563	**1.82** (1.37-2.43)	**2.57** (1.71-3.85)
80+	174	**2.92** (1.90-4.49)	**2.52** (1.50-4.25)
sex			
males	1879	1.00 (reference)	1.00 (reference)
females	1863	1.00 (0.88-1.15)	0.97 (0.81-1.17)
educational level			
low	1813	1.00 (reference)	1.00 (reference)
secundary	1377	**0.81** (0.70-0.94)	**0.80** (0.65-0.99)
high	552	**0.75** (0.61-0.94)	**0.64** (0.47-0.87)
type of health insurance			
public	2555	1.00 (reference)	1.00 (reference)
private	1187	**0.83** (0.71-0.98)	**1.26** (1.00-1.58)
number of conditions at start study			
0	1202	1.00 (reference)	1.00 (reference)
1	912	**1.25** (1.05-1.49)	**1.19** (0.93-1.54)
≥2	1628	**1.85** (1.57-2.19)	**1.51** (1.20-1.89)

high vs. low OR = 1.91 (1.53-2.38)). Responders were very well comparable to non-responders with regard to the number and type of prevalent disorders. Non-responders only showed psychological disorders more frequently than responders (this was not accounted for by any specific diagnostic category) (OR = 1.54 (1.16-2.04)). The non-response analysis was described more detailed in chapter six[48].

The basic characteristics

Table 1 shows that our population consisted of 50.2% men and 48.8% women. The mean age of the study population was 52.4 years (SD = 17.2). Almost half of the responders had a low level of education, well over a third had secondary education. The remaining 15% had a high educational level. Of our study population 68% had a public health insurance, 32% had private health insurance. Thirty-two percent of the subjects did not have any prevalent disease registered at the problem list at the start of the selection period, 24% had one prevalent disease and 44% had two or more diseases. The basic models, resulting from logistic regression analyses including age, sex, level of education, type of health insurance and number of diseases at the start of the study as independent variables and morbidity or multimorbidity as dependent variables, are shown in table 1. With exception of sex, significant effects and/or trends were identified for all variables.

All associations of the other possible determinants that were statistically significant for the occurrence of morbidity or multimorbidity, after adjustment for the basic variables are shown in table 2. Non-significant result are described in the text, but not included in the table.

FURTHER SOCIO-DEMOGRAPHIC VARIABLES - A vast majority of the responders (95%) was born in the Netherlands. Also most fathers and mothers of responders were born in the Netherlands (95% and 92% respectively). Only 0.9% of the fathers and 0.6% of the mothers were born outside Europe.

A vast majority reported being religious, the morbidity group more often than the healthy group (table 2). There was no additional relation however, with the presence of multimorbidity.

A little over 80% of the responders lived as a couple or as a family. Subjects with multimorbidity more often lived alone than subjects with monomorbidity. This difference did not remain,

TABLE 2: Relations between possible determinants and morbidity and multimorbidity, reported as crude and adjusted odds ratios (ORs) (and 95% condifence intervals). Only variables that were significantly related to either morbidity or multimorbidity when adjusted are reported.

	morbidity †		multimorbidity ‡	
	crude	adjusted*	crude	adjusted*
religion [N = 3,731/ N = 2,924]#				
any/no	**1.52** (1.21-1.91)	**1.29** (1.01-1.64)	1.22 (0.87-1.71)	0.99 (0.70-1.41)
occupational status§[N = 3,359/ N = 1,931]#				
positive/negative	**0.57** (0.50-0.66)	0.85 (0.70-1.03)	**0.44** (0.3-0.54)	**0.66** (0.51-0.86)
body mass index [N = 3,688/ N = 2,094]#				
≥27/<27	**1.41** (1.21-1.64)	**1.23** (1.05-1.45)	1.16 (0.95-1.41)	1.04 (0.84-1.28)
tobacco use[N = 3,692/N = 2,090]#				
smoked in past/never	**1.37** (1.17-1.61)	**1.36** (1.14-1.61)	1.16 (0.94-1.44)	1.12 (0.88-1.41)
smoke now/never	1.04 (0.88-1.22)	1.10 (0.93-1.31)	0.97 (0.78-1.22)	1.17 (0.91-1.49)
sports [N = 3,723/ N = 2,111]#				
yes/no	**0.71** (0.62-0.80)	**0.83** (0.72-0.95)	**0.81** (0.68-0.98)	0.96 (0.79-1.17)
long-term difficulties [N = 3,505/N = 1,974]#				
1/no	0.92 (0.76-1.10)	0.98 (0.81-1.18)	1.23 (0.95-1.59)	**1.37** (1.04-1.79)
≥2/no	0.94 (0.80-1.10)	1.10 (0.95-1.18)	0.93 (0.75-1.14)	1.21 (0.96-1.51)
life events 2 years previous to start of the study [N = 3,581/N = 2,034]#				
positive ≥ 1/0	0.87 (0.73-1.03)	**1.28** (1.05-1.56)	**0.52** (0.41-0.66)	0.77 (0.59-1.02)
negative ≥ 1/0	1.11 (0.95-1.31)	1.07 (0.91-1.26)	**1.27** (1.02-1.59)	**1.28** (1.02-1.62)
undetermined ≥ 1/0	1.05 (0.86-1.27)	1.08 (0.88-1.32)	1.08 (0.82-1.40)	1.02 (0.78-1.35)
health locus of control [N = 3,443/N = 1,926]#				
internal yes/no	**0.72** (0.63-0.83)	**0.78** (0.67-0.91)	**0.75** (0.62-0.91)	0.83 (0.68-1.01)
external yes/no	**1.41** (1.22-1.64)	1.09 (0.92-1.28)	**1.83** (1.49-2.24)	**1.38** (1.10-1.72)
chance yes/no	1.12 (0.97-1.29)	1.06 (0.92-1.23)	1.15 (0.95-1.40)	1.10 (0.90-1.34)
coping style [N = 3,414/N = 1,908]#				
active yes/ no	0.97 (0.80-1.17)	1.11 (0.91-1.36)	0.90 (0.69-1.16)	1.09 (0.83-1.43)
avoiding yes/no	**1.19** (1.02-1.38)	1.06 (0.91-1.23)	**1.29** (1.05-1.58)	1.15 (0.93-1.42)
social support yes/no	1.07 (0.93-1.23)	**1.16** (1.00-1.34)	1.11 (0.92-1.35)	**1.22** (1.00-1.50)
palliative yes/no	**0.86** (0.74-0.99)	**0.84** (0.73-0.97)	0.94 (0.77-1.14)	0.90 (0.73-1.10)
social network [N = 3,522/N = 2,007]#				
2/0-1	**0.69** (0.57-0.84)	0.88 (0.71-1.07)	0.80 (0.62-1.03)	1.06 (0.81-1.38)
3/ 0-1	**0.62** (0.50-0.75)	**0.80** (0.65-1.00)	**0.73** (0.56-0.96)	0.99 (0.74-1.33)
4/ 0-1	**0.51** (0.41-0.64)	**0.74** (0.59-0.94)	**0.72** (0.53-0.96)	1.10 (0.79-1.53)
≥5/ 0-1	**0.49** (0.39-0.62)	0.77 (0.59-1.01)	**0.32** (0.23-0.45)	**0.54** (0.37-0.77)

* adjusted for age, sex, socio-economic status, and the number of prevalent medical disorders at the start of the study

† subjects with one or more new diagnoses in the selection period versus subjects with no new diagnoses in the selection period

‡ subjects with two or more new diagnoses in the selection period versus subjects with one new diagnosis in the selection period

§ less than 8 hours (volunteer) job or study a week is defined as negative occupational status

\# number of subjects in the analysis for morbidity and multimorbidity respectively

however, after adjustment for the basic characteristics. Multimorbidity was not significantly related to the type of living arrangement. Parenthood was positively related to both morbidity and multimorbidity. These relations disappeared after adjusting for basic characteristics.

OCCUPATION - Fifteen percent of the subjects had a lower blue collar occupation, 17% a higher blue collar profession, 14% a lower white collar profession, 22% in a higher white collar profession. The remainder (32%) was classified as others; most of those were housewives and students. The occupational class did not show any relation with either morbidity or multimorbidity. Almost half of the responders did not have any regular occupational activities, for the multimorbidity group this was even 61%. This occupational status was related to both morbidity and multimorbidity; after adjustment only multimorbidity showed a statistically significant increase (table 2).

GENERAL HEALTH INFORMATION - The average length was 1.71 m (SD = 8.9 cm) and the average weight was 73.2 kg (SD = 13.7 kg). Subjects with a higher body mass index showed a significant higher occurrence of morbidity. For the occurrence of multimorbidity such a relation was not found (table 2).

HEALTH RELATED BEHAVIOUR - Of the responders 70% reported not to be a current smoker, 33% never smoked. Previous smoking (crude as well as adjusted) was related to morbidity, but not to multimorbidity (table 2). Current smoking was related to neither morbidity nor multimorbidity. According to the classification of the Royal College of General Practitioners, 7% of the responders were categorised as having a problematic alcohol intake. Based on crude data analysis subjects with problematic drinking showed lower occurrence of morbidity. This disappeared however, after adjustment. No relations were found with multimorbidity.

Fifty-nine percent reported not doing any sports. Those engaged in sports reported mostly cycling, swimming, fitness and aerobics, gym, walking, jogging, tennis and soccer, with a median time investment of 5 hours a week for those engaged in sports. Crude data analysis showed lower occurrence of both morbidity and multimorbidity among subjects who reported doing any sports. After adjustment the relation with morbidity sustained, the additional relation between sports and multimorbidity disappeared (table 2).

MEDICAL FAMILY HISTORY - Of the responders 35% reported parents, brothers or sisters having

suffered from cardiovascular disease before age 60. Cancer before age 60 was reported by 25%, death of parents, brothers or sisters due to a violent cause by 8%. None of these were related to the occurrence of multimorbidity. Only a family history of cardiovascular disease was slightly related to morbidity (crude OR = 1.16 (1.01-1.34)).

Overall 24% reported actual chronic disease or handicap in family members, with little differences between cases and controls.

LONG-TERM DIFFICULTIES - Out of the 17 categories responders mentioned 2.0 difficulties on average (SD = 2.1). Thirty percent of the responders did not report any long-term difficulties. Most frequently mentioned were problems regarding society (e.g., worrying about the environment, criminality, government policies), problems at work (e.g., difficult because of illness or fatigue, demanding job or job not satisfying), and sexual problems (e.g., conflicts with partner regarding sex, not having a sexual partner, or impotence). Crude data analyses did not show any differences. After adjustment, reporting one long-term difficulties was related to an increased risk for multimorbidity compared to reporting no long term difficulties (table 2).

LIFE EVENTS - In a two-year period previous to the case and control selection, 17% of the responders mentioned one or more positive life events, 22% reported at least one negative life event and 14% stated having at least one life event of undetermined significance. After adjustment, positive life events showed a positive relation with morbidity and a borderline significant negative relation with multimorbidity (table 2). The anticipated morbid effects of negative life events were not statistically significant for the occurrence of morbidity, but were so for the occurrence of multimorbidity.

HEALTH LOCUS OF CONTROL - Of the responders 64% could be characterised as having an internal locus of control, 35% as having an external locus of control, and 42% as having a chance locus of control (the different locus types are not mutually exclusive). The chance locus was not related to morbidity or multimorbidity. After adjustment only an internal locus of control was negatively related to the risk for morbidity and only an external locus was positively associated with the risk for multimorbidity (table 2).

COPING STYLE - An active coping style was identified in two thirds of the responders, with no statistically significant differences between the groups. About 15% of the subjects had an

avoiding coping style, which was related to both morbidity and multimorbidity without adjustment (table 2). Overall, 27% reported using a social support seeking coping style. Only after adjustment this coping style showed a significant higher risk for morbidity and multimorbidity. A palliative coping style was found in almost 40% of the responders. After adjustment, the use of a palliative coping style was negatively related to morbidity, but not related to multimorbidity.

SOCIAL NETWORK - On average, responders participated in 2.6 (SD = 1.5) social networks. Involvement in more social networks seemed to protect for morbidity. The relationship between social network participation and multimorbidity showed the same trend, but was after adjustment only statistically significant for participation in five or more networks.

VALUES - As expected, there were statistically significant differences between the theoretically conflicting values while compatible values did not differ significantly, indicating that there are no overall inconsistencies in the value systems. There were no differences between groups regarding inconsistencies in the value systems of cases and controls. Comparison of the appraisal of the separate values did not reveal any differences either.

Combined models

Backward stepwise multiple logistic regression analysis, starting with a model including all possible determinants as independent variables, resulted in fewer independent and statistically significant associations than the univariate analyses. Subjects with new morbidity were more likely to have a higher BMI, less likely to be active in sports, more likely to have smoked in the past, more likely to have had positive life events, less likely to have an internal locus of control, and more likely to have (had) family members with cardiovascular disease before age 60 than subjects without any new morbidity (table 3). Regarding the ORs for the additional dummies representing the item non-response, it is remarkable that there were inverse relations for BMI, positive life events and the value concept benevolence. The other dummies did not show inverse relations. Characteristics bivariately associated with morbidity but not confirmed in the multivariate analyses were: religion, social support coping style, palliative coping style and the size of social network.

TABLE 3: Results of multiple logistic regression analysis combining determinants of morbidity (≥ 1 new diseases vs. 0 new disease). Reported are odds ratios and 95% confidence intervals, N=3,745

variable	morbidity
age (in years);	
20-29	1.00 (reference)
30-39	0.96 (0.74-1.26)
40-49	**1.37** (1.04-1.79)
50-59	**1.43** (1.07-1.92)
60-69	1.10 (0.81-1.48)
70-79	**1.60** (1.15-2.23)
≥80	**2.76** (1.72-4.42)
sex; females vs. males	1.04 (0.89-1.20)
educational level;	
low	1.00 (reference)
secundary	**0.84** (0.72-0.99)
high	0.84 (0.67-1.07)
type of health insurance; private vs. public	0.85 (0.73-1.00)
number of conditions at the start of the study	
0	1.00 (reference)
1	**1.26** (1.05-1.51)
≥2	**1.84** (1.56-2.18)
occupational status; ≥8 vs. <8 hours a week	0.88 (0.72-1.06)
	0.68 (0.54-0.87)†
BMI; >27 vs. ≤27	**1.21** (1.03-1.42)
	0.56 (0.31-0.99)†
sports; yes vs. no	0.87 (0.75-1.00)
	0.38 (0.14-1.03)†
tobacco use;	
previous vs. never	**1.33** (1.12-1.58)
current vs. never	1.08 (0.90-1.29)
	1.21 (0.63-2.34)†
problematic alcohol intake; yes vs. no	0.77 (0.59-1.01)
	1.41 (0.85-2.32)†
positive life events; yes vs. no	**1.31** (1.07-1.60)
	0.76 (0.54-1.08)†
internal locus of control; yes vs. no	**0.79** (0.70-0.91)
	0.84 (0.58-1.20)†
cardiovascular disease in family; yes vs. no	**1.17** (1.01-1.35)
	1.27 (0.67-2.42)†
value 'benevolence';	1.09 (0.87-1.37)
important vs. not important	3.32 (0.33-33.5)
against principles vs. not important	0.61 (0.37-1.01)†
value 'security';	
important vs. not important	1.20 (0.97-1.49)
against principles vs. not important	1.00 (0.18-5.37)
	2.20 (1.26-3.85)†

† OR and 95% CI for dummy representing item-non-response

TABLE 4: Results of multiple logistic regression analysis combining determinants of multimorbidity (≥2 new diseases vs. 1 new disease). Reported are odds ratios and 95% confidence intervals, N=2,122

variable	multimorbidity
age (in years);	
20-29	1.00 (reference)
30-39	1.19 (0.80-1.78)
40-49	1.06 (0.72-1.56)
50-59	1.27 (0.84-1.92)
60-69	1.36 (0.88-2.09)
70-79	**1.79** (1.12-2.84)
≥80	**1.87** (1.04-3.36)
sex; females vs. males	0.91 (0.73-1.12)
educational level;	
low	1.00 (reference)
secundary	0.81 (0.64-1.03)
high	**0.60** (0.41-0.88)
type of insurance; private vs. public	1.22 (0.96-1.55)
number of conditions at the start of the study;	
0	1.00 (reference)
1	1.19 (0.92-1.54)
≥2	**1.49** (1.18-1.88)
occupational status; ≥8 vs. <8 hours a week	**0.63** (0.47-0.84)
	0.72 (0.49-1.06)†
occupational class;	
high blue vs. low blue collar	0.99 (0.71-1.38)
low white vs. low blue collar	0.99 (0.69-1.42)
high white vs. low blue collar	**1.48** (1.02-2.15)
others vs. low blue collar	1.31 (0.97-1.78)
	1.55 (0.87-2.77)†
active coping style; yes vs. no	**1.25** (1.01-1.55)
	0.62 (0.36-1.07)†
diseases in family; yes vs. no	0.90 (0.73-1.12)
	0.42 (0.22-0.79)†
hobbies; yes vs. no	1.11 (0.89-1.37)
	0.36 (0.14-0.96)†
network;	
2 vs. ≤1	1.28 (0.95-1.73)
3 vs. ≤1	1.26 (0.90-1.75)
4 vs. ≤ 1	1.46 (1.00-2.13)
≥5 vs. ≤1	0.73 (0.48-1.10)
	1.88 (1.07-3.29)†
external locus of control; yes vs. no	**1.40** (1.12-1.75)
	1.77 (1.02-3.08)†

† OR and 95% CI for dummy representing item-non-response

The occurrence of new multimorbidity compared to the occurrence of new monomorbidity was higher among responders who did not report (volunteer) work or study for at least eight hours a week, who had an active coping style, who belonged to a higher occupational class, and who had an external health locus of control. Item non-response of chronic diseases in the family, network and the external locus of control was significantly and positively related to multimorbidity (table 4). In contrast to the bivariate analyses, long term difficulties, negative life events and the social support coping style did not show independent associations. Check of the models without the additional dummy variables showed comparable direction and strength of associations, but showed wider confidence intervals.

Repeated analyses, excluding a relatively homogeneous subgroup of subjects diagnosed with diabetes mellitus (N=214), yielded the same results.

DISCUSSION

In this study we explored the associations between demographic, psychological, sociological and life style characteristics and the occurrence of morbidity and multimorbidity. Apart from identifying risk factors for morbidity, we had a special interest in the identification of characteristics that distinguish between the occurrence of morbidity in general and the occurrence of additional pathology (multimorbidity).

It is remarkable that risk profiles resulting from both the analyses per topic and the combined models show many differences for morbidity and multimorbidity. A number of variables showed an independent relation with the occurrence of multimorbidity, additional to the effect on morbidity. After adjustment for age, sex, socio-economic status and number of conditions present at the start of the study, subjects with multimorbidity less often reported having daily pursuits for at least 8 hours a week, reported a higher external health locus of control, more often had an active coping style and more often had a high occupational level than subjects with monomorbidity. None of the characteristics that was significantly related to multimorbidity was also statistically significantly associated to morbidity. This indicates that there are prominent differences between the profiles, the more so because of the overlap of the populations in the analyses (subjects with multimorbidity were also included in the so-called morbidity analyses).

Characteristics considered to be the basic variables were generally strongly related to both morbidity and multimorbidity. As in other studies concerning the co-occurrence of diseases, multimorbidity was found to be significantly related to rising age[7 49] and the number of chronic diseases already present before the study[50 51]. Previous findings of the relation between multimorbidity and sex are inconclusive[51 52]. In our study we found sex not to be related to the occurrence of multimorbidity. Our findings once more confirmed previous studies on the relation between socio-economic inequalities and differences in health[15 17 18]: a higher level of education was related to a decreased multimorbidity risk. However, we do not have an explanation for the (borderline significant) inverse effect of the type of health insurance on the occurrence of multimorbidity.

In the analyses that combined a number of independent variables we chose to include the missing values in the analyses as separate dummies, because case-wise deletion excluded a large and selective group of responders from the analyses. It appeared that the item non-response of psycho-social characteristics was not only related to the basic (demographic) characteristics, but also to other independent variables. Therefore, exclusion of subjects who omitted one or more items would possibly introduce a bias in the results. Including cases with missing values provides maximum use of the available data. The logistic models for morbidity and multimorbidity were duplicated, using the same patient characteristics but without the missing values. This showed relations in the same directions, but fewer were statistically significant, possibly due to a decreased number of subjects included in the analyses.

Furthermore, the associations found seem fairly robust and remained when a large and relatively homogeneous group (all subjects with diabetes mellitus) was excluded from the analyses.

In accordance with a previous study[7] a time frame of 3 years was used for the selection of cases and controls. According to Hinkle and Wolff[53] distribution of diseases is not random in time. They stated that there are marked differences in disease susceptibility for major as well as minor diseases that last for a number of years. Furthermore, a limited time frame for the selection of

cases and controls was chosen, because for a number of psycho-social characteristics the stability over time is not known, especially in case of events like serious diseases.

Until now little research has been published concerning the determinants of multimorbidity, but it has been hypothesised that psycho-social characteristics such as life events, coping style and size of social network[20 21] might be related to disease susceptibility, which could be linked to multimorbidity[11-13]. More empirical data are available concerning factors related to morbidity in general[16 54-56]. To our knowledge this study was the first one evaluating such a wide range of demographic, psychological, sociological and life style determinants on the occurrence of multimorbidity among such a large number of patients.

It was surprising to find only little association between (multi)morbidity and life events in the period before case selection. Especially the lack of association with negative life events is unexpected. A possible explanation for this finding is the variability of vulnerability for the emotional effects of negative life events. Such differences in vulnerability have been described between males and females[57], and do not necessarily run parallel to disease susceptibility. Also unexpected is the positive association between positive life events and morbidity, and the negative trend for multimorbidity. Previous studies on the health effects of positive life events are inconclusive. Brown[58] suggested that the adverse effect of positive life events might be confined to subjects with a low or negative self esteem. It has also been suggested[59] that - especially among the elderly - life events can be a consequence of a bad health status. Our study does not confirm these findings. Even the (crude) risks among subjects aged 60 years and older were not elevated.

Regarding smoking habits only an increased risk for morbidity was found among subjects who previously smoked. The fact that this association was not found for multimorbidity might be partly explained by a change of health related behaviour. Once people get diseased they are probably more likely to give up habits like smoking. Another explanation might be a selective survival: subjects who continue smoking possibly have a higher mortality risk. These

explanations should be tested using longitudinal data.

A similar mechanism may explain why no relation was found between problematic alcohol intake and either morbidity or multimorbidity. The frequent underrating of alcohol intake in interviews and questionnaires is an additional problem[60].

The associations found with the internal and external health locus of control are in line with our expectations, that subjects who feel in control of their health might actually have a healthier life style and therefore be at lower risk to get serious diseases. At the same time, it is possible that the occurrence of a serious disease or the exacerbation of a disease, that are not directly related to the subject's behaviour, lead to a more external locus of control belief[61].

Previous research on the relation between coping styles and health has revealed ambiguous results. It is however difficult to compare studies, because the coping concept has been operationalized in various ways. Penninx et al[62] reported an influence of mastery on mortality, indicating an increased mortality risk among subjects who feel little control over their life and who are more fatalistic. A similar effect of an active coping style on subjective health was found by Goldsmith Cwikel et al[63]. The study of Feij et al[40] on the relation between life events, coping styles and somatic and mental complaints however, did not supply any indications for a buffering effect of coping. In our study we only found an active coping style to be associated to the occurrence of multimorbidity, implying that subjects that are inclined to take a hand in case of problems are more susceptible to multiple pathology. Possibly, this is a result rather than a cause of multimorbidity, subjects with multiple pathology might be more apt to actively deal with problems because their (health) problems are less easy to avoid.

Because of the case-control design of this study, we had a single measurement of the patient characteristics. Some concepts - like coping style - are considered to be rather stable, but it can not be ruled out that these concepts change as a result of disease. Furthermore, there is a number of characteristics that might have a reciprocal relationship. For example: the internal and external health locus of control are likely to change as a result of hospital admission[38], but at the same time

it has been suggested that especially the internal locus of control may effect physical functioning[64] and health status[65]. Another example is the occupational status; e.g. being unemployed can be very stressful and therefore a risk factor for multimorbidity, but at the same time an increasing number of diseases makes it more difficult to continue work or study on a regular basis. Finally, there are characteristics that are most likely to be causes of multimorbidity, like long-term difficulties.

More in general it can be stated that a case-control study can trace relations and associations, but does not generally justify final conclusions regarding the direction between causes and effects. Associations found in this study however, can direct further prospective research regarding the determinants of multimorbidity.

We conclude that apart from the known and strong impact of age, number of prevalent diseases and socio-economic status, multimorbidity is associated with little of the patient characteristics included in our study: occupational status, external locus of control and active coping style. Still, there might be a specific profile for the susceptibility to multiple pathology, considering the marked differences between the associations found with morbidity and with multimorbidity. To gain insight in possible causal factors and preventive strategies, it is important to prospectively establish the impact of psycho-social factors on the occurrence of multimorbidity additionally. Furthermore, it is possible that specific disease categories, such as cardiovascular or locomotor diseases have more marked psycho-social risk profiles. It might therefore be useful to assess the impact of demographic, psychological, sociological and life style characteristics on the susceptibility of specific disease categories.

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CHAPTER 6

MORBIDITY IN RESPONDERS AND NON-RESPONDERS IN A REGISTER-BASED POPULATION SURVEY

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ABSTRACT

Background

Non-response analysis is often restricted to the influence of age, sex and socio-economic status on response status. In this study the health status of responders and non-responders was also compared.

Results

Responders were comparable to non-responders with regard to the number of diagnosed disorders as well as to the prevalence of disorders within body systems. Non-responders only showed psychological disorders more often.

Conclusion

It is useful to assess the relation between non-response and morbidity patterns in other studies as well, in order to detect selective non-response and bias.

INTRODUCTION

The use of postal questionnaires is common in epidemiological research. Non-response rates of 30%-40% are not unusual, and generally considered acceptable provided that the non-response is not obviously biased. However, in many studies little information concerning the non-responders is available. If evaluation is possible, it is often found that non-response is higher among the elderly, subjects with lower socio-economic status and subjects who live alone[1-3]. Responders and non-responders may also differ significantly with respect to other relevant characteristics, especially their health status, on which data are seldomly available. In this paper, we report on an analysis comparing responders and non-responders regarding morbidity.

SUBJECTS, METHODS, AND RESULTS

For a large register-based case-control study on determinants of multimorbidity, subjects were sampled from the Registration Network Family Practices (RegistratieNet Huisartspraktijken, RNH). The RNH is a computerised and continuous database in which 42 Dutch general practitioners (GPs) from 15 practices are participating. The GPs systematically collect all relevant chronic, recurrent or permanent health problems, which are coded according to the International Classification of Primary Care (ICPC)[4], as well as background variables of a general population of over 60,000 registered subjects. The quality of the data is ascertained by instruction and training sessions, regional consensus groups, quality control experiments and special software programs, such as automated thesaurus and automated checking for erroneous or missing entries[5]. Since all contacted subjects were sampled from the RNH, we were able to compare the morbidity of responders and non-responders. Using identification codes, data of non-responders could be analysed anonymously.

For this study, cases were defined as subjects aged 20 years or older who had two or more new diagnoses in a period of three years (sample N = 2,500). Controls were defined as subjects with no (sample N = 2,500) or only one new diagnosis (sample N = 1,250) in this period. Subjects were randomly sampled from this database. Because of the expected small number of elderly among the controls, a group of controls aged 60 years and older was added (N = 500). Seventy subjects could not be located in the participating practices, resulting in a eligible sample of 6,680

subjects.

Differences in socio-demographic characteristics between responders and non-responders were analysed using odds ratios (99% CI), adjusted for mutual interactions. Occurrence of disorders of the various body systems was dichotomised and their relation with response status was evaluated using logistic regression analysis. Reported are odds ratios (99% CI) adjusted for socio-demographic variables.

Before mailing the questionnaire, 512 subjects were excluded by their GP because they were illiterate, spoke little or no Dutch, or because of their mental or physical status. Another 55 subjects could not be included in the analysis, because the address information was incorrect. All other subjects (N = 6,113) received a postal questionnaire (24 pages A4 format), concerning demographics, life-style, personal and family medical history and psychosocial variables. A reminder was sent after three weeks. The questionnaire as well as the reminder was sent with a covering letter signed by the subjects' own GP and the researcher, kindly asking for co-operation and explaining the goal of the study.

A total of 3,744* subjects (61.2%) completed and returned the questionnaire. The response showed statistically significant relations with sex, age, education and living arrangement (table 1a). Comparison of morbidity showed that responders were comparable to non-responders with regard to the number of diagnosed disorders (p=.19). The prevalences of disorders within body systems were quite similar as well. Non-responders only showed psychological disorders more often (this was not accounted for by any specific diagnostic category) (table 1b).
Comparing the prevalences of forty randomly chosen specific disorders, only four showed a difference (with p<.01); two had a higher prevalence among responders, two among non-responders.

* After the non-response analyses, data from one delayed questionnaire were added. Therefore chapter 5 mentions 3745 reponders

TABLE 1: Percentage of subjects in the total sample (N = 6,680), among responders (N = 3,744) and non-responders (N = 2,936) with diagnosed disorders of the various body systems, and distribution of background features

(a) Patient characteristics	percentage of responders	percentage of non-responders	adjusted OR (99% CI)**
sex			
males	50.3	51.4	1.00 (reference)
females	49.7	48.6	**1.17** (1.01-1.36)
age (in years)			
20-29	14.3	10.4	1.00 (reference)
30-39	17.4	17.0	**1.36** (1.01-1.83)
40-49	16.2	18.3	**1.61** (1.19-2.17)
50-59	13.6	14.6	**1.60** (1.17-2.19)
60-69	15.6	20.0	**1.94** (1.43-2.62)
70-79	15.4	15.1	**1.51** (1.11-2.07)
≥ 80	7.4	4.7	1.03 (0.70-1.53)
living arrangement			
family	83.2	73.7	1.00 (reference)
alone	15.7	22.0	**0.74** (0.61-0.90)
home for the elderly	1.1	4.3	0.73 (0.39-1.35)
health insurance			
public	68.3	73.4	1.00 (reference)
private	31.7	26.6	0.98 (0.83-1.17)
educational level			
low	52.0	61.8	1.00 (reference)
secondary	36.7	30.5	**1.41** (1.19-1.67)
high	11.3	7.8	**1.91** (1.43-2.55)
(b) Body systems*	percentage of responders with at least one disorder	percentage of non-responders with at least one disorder	adjusted OR (99% CI)**
general and unspecified disorders	14.4	13.6	1.09 (0.88-1.34)
blood, blood-forming organs and lymphatics	2.1	2.0	1.40 (0.82-2.40)
digestive	13.7	14.8	1.00 (0.81-1.23)
eye (vision)	6.3	8.6	0.91 (0.68-1.22)
ear (hearing)	6.8	6.3	1.18 (0.88-1.58)
circulatory	29.8	32.7	0.98 (0.83-1.17)
musculoskeletal (locomotion)	28.2	26.8	1.12 (0.95-1.32)
neurological	7.8	8.5	1.01 (0.77-1.33)
psychological	5.3	10.2	**0.65** (0.49-0.86)
respiratory	16.8	16.8	0.99 (0.82-1.20)
skin	14.3	12.6	1.20 (0.97-1.49)
endocrine, metabolic and nutritional	17.3	17.7	1.00 (0.83-1.22)
urological	5.3	5.5	1.06 (0.76-1.48)
pregnancy, childbearing	0.3	0.3	0.72 (0.19-2.76)
female genital (including breast)	6.1	4.7	1.15 (0.83-1.61)
male genital	3.0	2.2	1.59 (0.99-2.56)

* according to the ICPC-classification

** the odds of responding is reported

COMMENT

It is often feared that the health status of responders and non-responders is different. Most studies do not have appropriate data to analyse this. Using a general practice based morbidity register as the sampling frame for this study, health status and non-response patterns could be studied extensively. This is a useful approach in morbidity databases, giving more insight into response patterns and possible non-response bias. Apart from psychological disorders no systematic differences, i.e. no non-response bias concerning the morbidity, could be identified. If the association between non-response and psychological disorders appears to be consistent in other studies, it is important to evaluate this in terms of selective non-response and bias, especially when psychologically related variables or outcome measures are used.

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CHAPTER 7

PSYCHO-SOCIAL DETERMINANTS OF MULTIMORBIDITY:
a prospective study

Submitted as:

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Psycho-social determinants of multimorbidity: a prospective study.

ABSTRACT

Objective

Aim of this study is to get a profile of patients who are vulnerable to get multiple chronic, recurrent or high-impact diseases in a limited time period. We studied the incidence rates of morbidity and multimorbidity, and the influence of psycho-social characteristics on their occurrences.

Method

A cohort of 3,551 subjects was followed for a period of two years. At baseline psycho-social characteristics were measured. During follow-up new morbidity (defined as the occurrence of one or more diseases during follow-up) and multimorbidity (defined as the occurrence of two or more diseases during follow-up) were registered. The relations were evaluated using multiple logistic regression analysis.

Results

Clear relations between basic characteristics (age, sex, educational level, type of health care insurance and number of prevalent diseases at baseline) and morbidity and multimorbidity were observed. After adjustment for these variables, a high internal locus of control belief was found to be protective for the occurrence of morbidity. Characteristics specifically protective for the occurrence of multimorbidity as compared to monomorbidity were: a high internal locus of control belief, the occurrence of life events of undetermined significance, living as a couple or in a family as compared to living alone, and a large social network.

Conclusions

Apart from the well described influences of age, socio-economic status and previous health status on health and illness, there were little indications for an increased risk of morbidity related to psycho-social factors. There seem to be some characteristics that discriminate between the occurrence of only one disease and new multimorbidity during follow-up.

INTRODUCTION

Many people are suffering from multiple diseases. This health problem, called multimorbidity[1], is a population-wide problem. Although far more frequent among the elderly, also among people under age 20 a considerable prevalence of multimorbidity was found (10%), using a broad nosological spectrum of chronic, recurrent and high-impact diseases[2]. The general practitioner (GP), who acts as a gate-keeper in the Dutch health care system, is often confronted with complex health care situations of patients who have co-occurring diseases. Generally it is not clear why some patients have a number of diseases at the same time or in a limited time period and others do not. Therefore, apart from the more classical approach studying the aetiologies of specific diseases, there is an increasing interest in the determinants of general disease susceptibility, disease-prone personalities and frailty[3-8]. Syme and Berkman[9] suggested to study a generalised body response in relation to psycho-social variables instead of specific diseases.

Because no studies on determinants of multimorbidity are available yet, possible determinants of multimorbidity have to be derived from determinants of health in general and from suggestions done by previously mentioned researchers and other experts. This kind of research aims at the improvement of profiles of patients who are at higher risk of getting multiple disease and may facilitate the development of future preventive interventions as well as more effective prediction and monitoring of patients.

Previously, we did a cross-sectional[2] and a retrospective study (chapter 5) on this subject. These studies showed a strong increase of multiple disease with rising age and an increased risk for subjects with a lower socio-economic status. When adjusted for the socio-demographic variables, the occurrence of two or more diseases in a three-year period (multimorbidity) compared to the occurrence of just one disease was found to be related to certain coping styles, an external health locus of control, long term difficulties, negative life events and a smaller social network. Regarding psycho-social characteristics, the occurrence of any morbidity was related to positive life events, certain coping styles, social network and the internal health locus of control. However, cross-sectional and retrospective designs do not allow conclusions regarding causality. Therefore, we started a prospective study, using the data from the retrospective study as a baseline measurement.

This report describes the results of a 2-year follow-up of this study population: a prospective study on the influence of psycho-social characteristics on the occurrence of morbidity and multimorbidity. The main research questions for this study were: 1) what is the incidence rate of morbidity (defined as one or more new disease) and multimorbidity (defined as two or more new diseases) in a period of two years? and 2) what is the influence of coping style, life events, health locus of control, long-term difficulties, type of living arrangement and social network on the occurrence of morbidity and multimorbidity in a period of two years after baseline measurement?

METHODS

Context

This study was carried out within the context of the Registration Network Family Practices (RNH). This is a continuous and computerised database in general practice with a target population of about 100,000 people. All relevant health problems are registered in the database. Within the RNH, a health problem is defined as 'anything that has required, does or may require health-care management and has affected or could significantly affect a person's physical or emotional well-being'. Health problems are registered on the problem list if they are permanent (no recovery expected), chronic (duration longer than 6 months), recurrent (more than 3 recurrences within 6 months) or when they have lasting consequences for the functional status or prognosis of the patient. Problems are coded using the International Classification of Primary Care (ICPC)[10], with the criteria of the International Classification of Health Problems in Primary Care (ICHPPC-2) for diagnoses[11]. The data are continuously updated and cumulated for each patient. Population membership only ends by migration or death.

The quality of the data is ascertained by instruction and training sessions, regional consensus groups, quality control experiments and an automated thesaurus and automated checking for erroneous or missing entries[12]. Reliability and completeness has been shown by comparisons between RNH's cancer data and the data of the regional Cancer Registry[13] and between RNH's epilepsy data and the Maastricht Epilepsy Case Register[12].

For this study, morbidity and multimorbidity are operationalized using health problems registered in the RNH, representing diagnostic codes, in accordance with our previous research

on this subject [2].

Questionnaire

For the retrospective study 3,745 subjects completed a questionnaire asking for demographic characteristics, and a number of life style, psychological and sociological characteristics[14]. This study focuses on six psycho-social concepts that proved relevant in the retrospective study: coping styles, health locus of control, life events, long term difficulties, type of living arrangement and social network.

Coping can be described as the stress management or the adaptive reaction, thoughts and actions that are used to stand up to a stressor[15]. It was measured using the Utrecht Coping List[16] [17], distinguishing four styles: active coping style (implying that a subject generally takes action in case of problems), seeking social support (subject is tempted to share problems with others), denial/avoidance (subject tries to stay away from any trouble and is passive in case of problems) and a palliative coping style (implies that a subject focuses on non-problem related things). In the analyses a dichotomised score, based on the contents and distribution of the score, was used.

The health locus of control measures the extent to which individuals attribute their health to themselves (internal), to powerful others like doctors (external) or to chance or destiny (chance). The internal, external and chance locus were measured using the validated Dutch version[18] of the Multidimensional Health Locus of Control by Wallston et al[19], and were analysed using a dichotomised score, based on the contents and distributions of the scores.

Life events were measured using the VRMG (Questionnaire Recent Events; Vragenlijst Recent Meegemaakte Gebeurtenissen)[20]. Subjects were asked to mark the items applicable to them during the last five years and to date those items. Subjects could score up to five positive life events, twenty-one negative life events, and eight life events of undetermined significance.

The Long-term Difficulties Questionnaire[21], used for measuring chronic stress[22], related to problems with housing, work, school, finances, relationship with family and friends and problems with societal developments. In agreement with previous research we added a question about difficulties concerning leisure activities[23]. In the analyses we used the number of relevant problems reported; none, one, two or more. Health related problems were not used in the

analyses, because of dependence to the outcome measure (morbidity registered by the GP).

The type of living arrangement was categorised in three groups: those living as a couple or a family, those living alone and others (e.g., living in a home for the elderly).

Seven items were selected as indicators for the subjects' social network: type of living arrangement, paid job, volunteer job, study, membership of a union, participation in team sports, and participation in joint leisure interests. The maximum score on social network was nine. Other community studies on social integration and e.g. mortality have used similar measures[24].

Follow-up

For the evaluation of the longitudinal impact of the psycho-social characteristics, morbidity was measured during two years following the baseline measurement (January 1996 - December 1997). Data could be matched for 3,551 (94.8%) of the 3,745 original responders (table 1). Of those, 91 subjects died during follow-up; they were categorised as having had new (multi)morbidity.

TABLE 1: Basic patient characteristics at baseline (N=3,551)

characteristic		%
sex	male	50.7
	female	49.3
age (in years)	20-29	9.3
	30-39	16.7
	40-49	18.7
	50-59	14.9
	60-69	20.5
	70-79	15.2
	≥80	4.7
health insurance	public	68.1
	private	31.9
education	low level	49.2
	secondary	36.4
	high level	14.4
number of diseases at the start of follow-up	none	21.9
	one	21.0
	two or more	57.1

Population

Socio-demographic characteristics of our study population are described in table 1. The population consisted of 1800 (50.7%) males and 1751 females, the mean age was 52.9 years (SD 17.0). The majority had a public health care insurance. Almost half of the responders had a low educational level, just over one third had secondary education and the others had a high educational level. The mean number of prevalent diseases at baseline was 2.5 (SD 2.4), with 57.1% having two or more prevalent diseases.

Analyses

Descriptive statistics are reported with respect to new morbidity and new multimorbidity in the study population. To evaluate the impact of possible determinants on the occurrence of new morbidity and new multimorbidity, variables were tested using odds ratios (ORs), calculated by means of multiple logistic regression analyses. All models were adjusted for the influences of age, sex, educational level, type of health insurance and number of prevalent diseases at baseline. Independent variables were successively: coping style, health locus of control, long-term difficulties, life events, type of living arrangement and social network. Morbidity and multimorbidity were used as the dependent variables respectively. For analysing the occurrence of morbidity, subjects with one or more diseases during follow-up were compared to subjects with no new morbidity; for studying multimorbidity, subjects with two or more new diseases during follow-up were compared to subjects with exactly one new disease, to establish the additional effects on multimorbidity as compared to morbidity. Apart from this, one disease category - the psychological diseases - was evaluated separately, because these diseases are possibly more likely to be related to psycho-social characteristics.

All analyses were carried out using the programmes 2D and LR of BioMedical Data Package (BMDP)[25].

RESULTS

The mean number of new diseases registered on the problem list between January 1996 and December 1997 was 0.4 (SD 0.8, range 0-8), with 73.9% and 91.4% of the subjects not getting

morbidity and multimorbidity respectively, during the follow up period.

The 'basic model' (table 2) showed that the risk of getting two or more new diseases as opposed to getting one new disease was increasing with age, and higher for men compared to women. The occurrence of new morbidity (subjects with one or more new diseases compared to subjects with no new disease during follow-up) was related to an increasing age, a low level of education, was higher for subjects with a public compared to a private health insurance, and was increased for subjects who already had multimorbidity at baseline compared to those who did not.

TABLE 2: Relation between 'basic variables' and new morbidity and new multimorbidity in the follow-up period (adjusted ORs and 95% CIs)

characteristic		≥1 vs. 0 new diseases OR (95% CI)	≥2 vs. 1 new diseases OR (95% CI)
age (years)	20-29	1.00 (reference)	1.00 (reference)
	30-39	0.85 (0.58-1.26)	2.22 (0.67-7.32)
	40-49	1.18 (0.81-1.70)	**3.67** (1.21-11.2)
	50-59	**1.82** (1.26-2.63)	**7.44** (2.50-22.1)
	60-69	**2.12** (1.48-3.02)	**6.92** (2.36-20.3)
	70-79	**3.02** (2.10-4.36)	**7.34** (2.50-21.6)
	≥80	**5.46** (3.48-8.58)	**10.4** (3.37-32.0)
sex	females vs. males	0.93 (0.80-1.09)	**0.59** (0.45-0.77)
educational level			
	low	1.00 (reference)	1.00 (reference)
	secondary	**0.82** (0.69-0.99)	0.78 (0.57-1.08)
	high	**0.72** (0.54-0.95)	0.73 (0.44-1.23)
type of health insurance			
	private vs. public	**0.81** (0.67-0.98)	0.97 (0.69-1.37)
number of prevalent diseases at start follow-up			
	0	1.00 (reference)	1.00 (reference)
	1	1.02 (0.77-1.34)	1.30 (0.72-2.33)
	≥2	**1.98** (1.58-2.48)	1.52 (0.94-2.45)

After adjustment for these basic variables, only a few of the psycho-social characteristics showed significant relations with the occurrence of either morbidity or multimorbidity (table 3). New morbidity was only found to be more common for subjects with a low score on the internal locus of control. For multimorbidity we found a higher risk during follow-up among: subjects with a

low score on the internal locus of control compared to those with a high score, among subjects who had no life events of undetermined significance compared to subjects with one or more of those life events, among subjects living alone as compared to those living as a couple or in a family, and for subjects with a small social network as compared to those with a large social network (≥5).

TABLE 3: Relation between psychological characteristics and the occurrence of new (multi)morbidity, adjusted for age, sex, social economic status and number of prevalent diseases at the start of follow-up (ORs and 95% CIs)

characteristic		≥1 vs. 0 new diseases	≥2 vs. 1 new disease
coping styles			
active tackling	yes vs. no	0.90 (0.72-1.12)	0.93 (0.64-1.35)
avoiding	yes vs. no	1.06 (0.89-1.27)	0.97 (0.71-1.33)
palliative	yes vs. no	1.00 (0.84-1.19)	0.74 (0.54-1.01)
seeking social support	yes vs. no	0.98 (0.82-1.16)	1.19 (0.87-1.63)
life events			
positive	yes vs. no	1.04 (0.82-1.32)	1.04 (0.63-1.71)
negative	yes vs. no	1.00 (0.85-1.18)	1.33 (0.99-1.78)
undetermined	yes vs. no	0.93 (0.74-1.17)	**0.59** (0.38-0.90)
locus of control			
external	yes vs. no	1.14 (0.95-1.38)	1.05 (0.76-1.45)
internal	yes vs. no	**0.82** (0.69-0.97)	**0.73** (0.54-0.99)
chance	yes vs. no	0.95 (0.80-1.12)	1.29 (0.95-1.75)
long-term difficulties	0	1.00 (reference)	1.00 (reference)
	1	1.02 (0.82-1.28)	1.03 (0.71-1.49)
	≥2	0.99 (0.82-1.21)	0.81 (0.58-1.14)
type of living arrangement			
	couple/family	1.00 (reference)	1.00 (reference)
	alone	0.93 (0.76-1.15)	**1.48** (1.03-2.13)
	others	1.51 (0.91-2.53)	0.66 (0.27-1.62)
social network	0/1	1.00 (reference)	1.00 (reference)
	2	0.94 (0.75-1.18)	0.88 (0.61-1.28)
	3	1.20 (0.95-1.53)	0.75 (0.50-1.12)
	4	0.98 (0.74-1.29)	0.73 (0.44-1.22)
	≥5	1.07 (0.78-1.49)	**0.41** (0.21-0.83)

Forty-three subjects had a new psychological disease during follow-up. All those subjects had at least one additional disease during follow-up. There were no relevant or statistically significant differences between subjects with and without psychological diseases regarding the psycho-social

characteristics.

DISCUSSION

In this study we evaluated the impact of psycho-social characteristics on (multi)morbidity during a follow-up period of two years. When adjusted for basic socio-demographic variables and health status at baseline, morbidity was only found to be related to internal locus of control. Multimorbidity during follow-up showed relations with the internal health locus of control, life events of undetermined significance, the type of living arrangement and the size of social network. So, whereas there were little indications for an increased risk for incident morbidity related to psycho-social factors, there seemed to be some characteristics that discriminate between the occurrence of only one disease and new multimorbidity during follow-up. First, we will discuss each of the psycho-social characteristics separately related to previous findings from our own research and other studies. Then conclusions will be integrated.

Life events

In the retrospective study, relations were found between the occurrence of negative life events and the risk of multimorbidity (OR = 1.28 (1.02-1.62)). In the longitudinal analyses the same trend was seen, with only borderline significance. Subjects who had experienced life events of undetermined significance, such as moving house or retiring, showed to be far less at risk to have two or more new diseases registered during follow-up. This is an unexpected and so far unexplained finding.

Several reports describe a significant relation between life events and health, often using self-reported or subjective health as outcome measure[26-31]. Some studies used more objective health related data obtained from a physician's registration or examination, and did not report any significant relations[32 33]. Only one study described a significant relationship between life events and mortality during a 7-year follow-up[34]. Additional analyses of our data did not show any significant relation between life events and mortality during the follow-up period.

Long-term difficulties

Chronic stress - operationalized as long-term difficulties - was hypothesised to be related to the onset of (chronic) diseases. The direct relation between long-term difficulties and health has not been studied before. There is however, a number of studies describing the relationship between stress and the immune system, studying the indirect effects on health[35 36]. The relation between long-term difficulties and health, that was also seen in our retrospective study, was not confirmed using prospective data. Possibly the likelihood of reporting problems is higher in periods of bad health. Furthermore, it is possible that long-term difficulties, affecting the immune system, have effects on specific (clusters of) diseases, but do not have an overall effect on the occurrence of chronic, recurrent and high-impact diseases.

Coping

Previous studies report ambiguous results regarding the relation between health and coping styles[15 37 38]. In the retrospective analyses an increased risk for multimorbidity was only found to be related to a seeking social support coping style. The prospective analysis revealed the same trend, but not statistically significant. This implies that the seeking social support style and multimorbidity most likely have mutual influences.

Health Locus of Control

The association between external locus of control and multimorbidity as found in the retrospective study was not confirmed in the prospective study. It is therefore more likely that the external locus is a consequence of multimorbidity rather than a cause. It has been previously described that a long-term experience with illness may influence one's expectancies for control over the illness; periods of exacerbation and remission, not related to the subject's behaviour, may lead to more external locus of control beliefs[39].

The relation between a high score on the internal locus and (multi)morbidity identified in the retrospective study was confirmed, indicating that subjects who believe they are in control of their own health, actually develop fewer diseases. It is however possible that the internal health locus of control also changes as a result of new disease. Further research is needed to establish the exact

nature of this relation. If a more internal locus of control is causally related to subsequent (multi)morbidity, we suggest to develop and evaluate behavioural therapies to strengthen the internal locus of control beliefs. It has been suggested[40 41] that the effectiveness of an internal locus of control belief might be reserved to specific subgroups, while others may have more benefit using an external locus of control. Furthermore, implementation of such an intervention might be difficult and is probably easiest amongst subjects who already have relatively internal beliefs. Only a few papers have been published, mentioning the problems and possibilities of training specific locus of control beliefs[42-44].

Living arrangement

In previous cross-sectional research, Joung et al found that subjects living alone had higher self-reported morbidity rates than subjects cohabiting or living with parents[45]. In our retrospective study no association between the type of living arrangement and the occurrence of morbidity or multimorbidity was found. During the follow-up however, it showed that subjects living alone were more at risk for new multimorbidity.

Social network

Social networks of people are often thought to be causally related to health status. Previous research has shown that a better social integration is related to a lower mortality rate[46 47]. Conclusions regarding social network and somatic diseases are inconclusive[24 29], while its protective influence on mental health is more clear[48 49]. From our data it seems that a large social network is not protective for morbidity in general. A considerable social network, however, might be protective for the occurrence of additional diseases. This can be partly explained by detection bias: subjects with new morbidity and a small social network might show more help seeking behaviour than those with a larger social network. Therefore, they might have a higher chance that diseases are detected.

General

Although reported separately, discussions about the concepts measured in this study often

overlap. E.g., Penninx et al[38] and Goldsmith Cwikel et al[37] measured coping styles, which are conceptually very similar to the locus of control concept by Wallston and Strudler Wallston[19]. Also, both life events and long-term difficulties can produce stress-related consequences, although the onset and duration of the stress might be different. The type of living arrangement is often seen as a part of the social network.

Combining the different concepts in our study and taking the results of our analyses into consideration, we conclude that a subject most resistent to multimorbidty could be described as a young initially healthy women, living with a partner or in a family and falling back on a relatively large social network. She would have a strong internal locus of control and a number of life events of undetermined significance. In summary, she would be a self-assured woman, well embedded in her social environment.

For this study a general practice based population was used as a sampling frame. Using such a population has important advantages. Results are far more generalisable than for studies in highly selected populations, and a broad spectrum of diseases can be studied, because such a data base reflects the actual morbidity in the general population. It is possible that there are associations that are specific to (clusters of) diseases. Those might be more difficult to demonstrate since sufficient numbers on specific diseases are required. Therefore, further disease specific studies are needed.

In this study psychological characteristics were only measured at baseline. It can not be excluded that some characteristics, like coping styles and the health locus of control change as a result of the health status. Therefore, in future prospective research repeated measurement of these characteristics would be more informative.

Previous studies on the relations between psycho-social characteristics and health regularly used self-reported or subjective health measures. Psychological characteristics are often found to be related to subjective health; our study provides fewer indications that many of those characteristics are causally and substantially related to the occurrence of chronic, recurrent and high impact diseases, as registered and reported by the GP. Schrader[50] already described such a discrepancy between objective and subjective medical comorbidity of depression. Still, we found

multimorbidity as registered by the GPs to be related to an internal locus of control, life events of undetermined significance, type of living arrangement and the size of social network.

It is also possible that psycho-social measures have a larger effect on the occurrence of diseases in specific categories, e.g. psychological diseases. We did not find relevant or statistically significant differences between the occurrence of psychological morbidity and either of the psycho-social variables, but the group with new psychological diseases was rather small and very homogeneous as to our main outcome measure - all subjects had new multimorbidity.

The results from this study suggest that there might be some possibilities to reduce the amount of new chronic, recurrent, and high impact morbidity, for example by stimulating subjects to participate in network and training of the internal locus of control[42 51]. To our knowledge the effects of such interventions have hardly been studied.

To further evaluate the long-term influences of psychological characteristics on the occurrence of diseases, we suggest to evaluate these characteristics using a longer follow-up period with repeated measurements of the characteristics, as well as evaluation in terms of specific clusters of diseases.

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CHAPTER 8

GENERAL DISCUSSION

INTRODUCTION

In this chapter the main results of this thesis will be reported. Furthermore, conclusions of the different parts will be integrated, and methodological strengths and weaknesses as well as the interpretation of the results are discussed. Finally, conclusions are drawn and translated into recommendations for practice and further research.

The studies reported in this thesis were guided by four key questions:

- How can comorbidity and multimorbidity be defined and operationalized?
- What are the main relevant methodological and analytical issues with respect to research on comorbidity and multimorbidity?
- What are the incidence and prevalence rates of multimorbidity in the general population?
- What are the major determinants of multimorbidity, with specific focus on demographic, psycho-social and life style characteristics?

MAIN RESULTS

Reviewing the literature on multiple pathology, a striking disagreement became manifest on the terminology with respect to the co-occurrence of diseases and the way this is operationalized for research purposes. As a result, different studies on this subject can hardly be compared. In order to diminish indistinctness we proposed to distinguish between two terms:

1. comorbidity with the original definition by Feinstein[1]: 'Any distinct additional entity that has existed or may occur during the clinical course of a patient who has the index disease under study';
2. multimorbidity defined as: 'the co-occurrence of multiple chronic or acute diseases and medical conditions within one person'.

Other varying characteristics of former studies concentrate on the type of diseases (e.g., acute, chronic), and the study population (e.g., general population versus hospital population, age categories).

Prevalence rates of multimorbidity as reported in previous studies varied between 1% to

over 50%. Some authors suggest causal relations between the occurrence of multimorbidity and a number of characteristics, but only a very few reported empirical studies.

Comparing different designs and operationalizations, we concluded that for an appropriate study of comorbidity and multimorbidity it is important to make some explicit choices:

- Is the study focused on comorbidity or on multimorbidity? This choice refers to the distinction described previously; does the main research question focus on diseases additional to an index disease (comorbidity) or on the co-occurrence of diseases in general (multimorbidity)?
- Is it appropriate to exclude certain (types of) diseases for a particular study? The number and type of diseases (in particular differentiating between chronic and acute diseases) included in a study have major impact on the incidence and prevalence rates of co-occurring diseases found and might also influence other relations under study.
- Especially relevant in comorbidity and multimorbidity research is the operationalization of diseases and disease entities. In specific studies it can be useful to define combinations of diseases that are pathophysiologically related (e.g., asthma and atopic dermatitis), as one disease. For other studies (e.g., measuring the number of complications of a certain disease), it might be more useful to count separate diagnoses. Furthermore, one has to realise that in multimorbidity research - covering a broad nosological spectrum - there are very few combinations that are exclusively related to one another and not to other diseases.

Analysing the co-occurrence of diseases, a number of strategies is available. Most commonly performed are descriptive analyses of the prevalence rates of co-occurring diseases. Furthermore, there are methods to evaluate the amount of clustering of diseases at a population level, or subgroups of the population. The first method is based on a comparison of the actual (observed) and the statistically expected amount of clustering. The amount of clustering beyond chance can then be expressed as a ratio of the observed and expected numbers. Interpretation of this ratio might be difficult, because for many combinations of diseases the assumption of statistical independence is known not to be justified. Still, this measure can be very useful, e.g. for comparison of the amount of clustering in different

subgroups of the population.
Another method to evaluate clustering of diseases is the calculation of relative risks or odds ratios. An important advantage of using odds ratios is the relative simplicity to adjust for confounding variables, using multiple logistic regression analysis.

Analysing data from the Registration Network Family Practices (RNH), using a broad nosological spectrum, we found high prevalence rates of multimorbidity among all ages in the general population. Furthermore, the prevalence rate of multimorbidity was found to be higher among females compared to males, increasing with age, decreasing with higher educational levels, higher for subjects with public as compared to those with private health insurance, and higher for subjects living in a home for the elderly compared to those living in a family. For the one-year incidence rate of multimorbidity a higher risk was found for the elderly, subjects with a public health insurance, and subjects that had two or more diseases at baseline. Statistical clustering of diseases was found for both sexes and all age categories, but was decreasing with age.

Evaluation of the influence of other characteristics was focused on psychological, sociological, life style and demographic characteristics and was performed using a nested case-control study, and a subsequent two-year follow-up study.
Analyses of data from the case-control study showed that, apart from the known strong impact of age, socio-economic status and the number of prevalent diseases at baseline, multimorbidity was associated with few of the studied characteristics. A logistic regression model combining all factors associated, only showed multimorbidity to be more frequent among subjects who did not report (volunteer) work or study, subjects with an active coping style, subjects with a high occupational class and subjects with an external locus of control.
The two-year follow-up of this population was focused on the psycho-social factors. Adjusting for the demographic characteristics and prevalent morbidity at baseline, characteristics found to be protective for the occurrence of new multimorbidity, as compared to monomorbidity, were: a high internal locus of control belief, the occurrence of life events

of undetermined significance, living as a couple or in a family as compared to living alone, and a large social network.

METHODOLOGICAL CONSIDERATIONS CONCERNING THE EMPIRICAL STUDIES

Operationalization of multimorbidity

For the operationalization of the empirical studies we choose to study multimorbidity, not comorbidity, because our main interest was to gain insight into disease clustering, general disease susceptibility and factors influencing those. Multimorbidity can be seen as an expression of general disease susceptibility.

For the assessment of prevalent multimorbidity, we counted the number of diagnoses registered by the GP. All subjects who had two or more prevalent diseases were defined as having multimorbidity, in accordance with previous studies on multiple pathology[2-6]. Definition of multimorbidity for the case-control study was slightly different. In agreement with previous research by Seeman et al[7], we selected cases and controls based on the occurrence of multiple new diseases during a three-year period. The main reason for different operationalization lies in differences between the factors under study. Socio-demographic factors are rather stable over time; for psycho-social factors this can not be presumed. Had prevalent multimorbidity been the criterion for the case selection of this study, relations might have been obscured because of the possible instability of the studied factors.

Assessment of multimorbidity was based on a count of diseases, without giving weights or severity scores to diseases[8 9]. Our main outcome measure was disease susceptibility, trying to find general mechanisms that trigger people to develop multiple chronic, recurrent or high impact diseases (major illnesses). Alternative operationalizations could have been: minor and major illnesses known by the doctor, all health related complaints and diagnoses registered by the GP, or health status or number of diseases as reported by the responders. Those alternatives might have resulted in quite different study populations, and might therefore have resulted in different risk profiles. E.g., biological circumstances identified and classified by the health care disciplines as diseases can be experienced by individuals and their families and social groups as illness. However the correspondence between medical disease and personal

illness is by no means exact[10].

Validity and precision of the data

THE REGISTRATION NETWORK FAMILY PRACTICES

The basic datasystem for all empirical studies reported in this thesis is the Registration Network Family Practices (RNH). The reliability of the morbidity data was shown by previous research[11 12] and there is a continuous ascertainment of the quality of registration[12].

Registration of the patient background characteristics in the RNH also seemed reliable, when compared to data available from questionnaires[13]. Especially in case of rather stable characteristics (e.g., educational level of subjects aged 25 or older), the level of agreement of data registered by the general practitioners (GPs), and data provided by the patients is high. In case of less stable characteristics, like the type of living arrangement, it seems advisable to obtain recent information from the responders.

For the analysis of the prevalence rate of multimorbidity (chapter 4), only so-called 'active diseases' were included. Once a disease is registered as active, it remains active until the GP 'blinds' it. For certain diseases registered on the problem list, like dyspepsia or migraine, it is possible that those unjustly remain registered as active diseases. This may be due to the fact that it is not brought to the GP's attention that the patient does not need any subsequent treatment, medication or disease monitoring. As a result, there might be a slight overestimation of the prevalence rate of multimorbidity. The estimation of incident (multi)morbidity is not influenced by this.

On the other hand, the GP can only register those diseases that are brought to his attention. This could induce an underregistration of the actual diseases, and result in an underestimation of incidence and prevalence rates of morbidity and multimorbidity. This has been described as the iceberg phenomenon[14], indicating that the majority of pain and physical inconveniences, some possibly related to serious disease, are not known by the GP. In a multiple case study on non-attendance, Beukema-Siebenga[15] found that among subjects who did not contact their GP for five years or longer, 40% reported regular health problems. However, the most commonly reported health problems in that study were backaches, colds, nervousness, headaches, and

sleeplessness. Those are types of health problems that are not included in the studies reported in this thesis; for these studies, all codes representing symptoms and complaints as well as pregnancy and delivery without pathology, double codings, test results not leading to a diagnosis, variations of normal functioning, superficial injuries and risk factors were excluded.

In conclusion we believe that the RNH is a sufficiently valid and precise database for both the analyses of the incidence and prevalence rates of multimorbidity and their associations with patient background variables, and as a sampling frame for the case-control study with its subsequent follow-up.

THE QUESTIONNAIRE

The contents of the questionnaire that was used for the case-control study and as a baseline measurement for the follow-up was very diverse, because of the explorative character of these studies. Regarding the study of multiple pathology, there is an ongoing discussion as to whether it is more profitable to use a general approach, as is presented in this thesis, or a disease specific approach. Arguments for disease specific analyses mainly relate to the expected disease specific mechanisms. However, evaluating 50 years of epidemiological research in the area of coronary heart disease (which is one of the most successful areas in this regard), Syme[16] concluded this has yielded a number of disease specific aetiologies, that together explain only about 40% of the coronary heart diseases that occur, leaving 60% unaccounted for. Already in 1976 Cassel[17] stated that there is a remarkably similar set of risk factors that relate to very diverse disease entities, implying the usefulness of factor specific research additional to disease specific research.

For the studies reported in this thesis, choices had to be made regarding inclusion and exclusion of topics. Those topics that the research group thought to be most plausible and promising were included.

The first choice to be made in this regard was a more general one: whether to focus on psycho-social, or e.g., immunologic or genetic characteristics. The influence of demographic characteristic on health status, morbidity and mortality has been studied extensively and has

been described in previous reports. Therefore the inclusion of those characteristics was beyond dispute.

The influence of immunologic characteristics has been explored simultaneously to this study, using data from the RNH [unpublished data]. Patients with one or more (out of twelve) immunologically related disorders were classified as having an impaired immunologic system. The occurrence of multimorbidity in patients with a known immunologically related disorder was compared to the occurrence of multimorbidity in patients without such a disorder. Analyses were performed overall, as well as separately for four types of immunologically related disorders: immediate hypersensitivity reactions, antibody dependent cytotoxic hypersensitivity, complex-mediated hypersensitivity, and cell-mediated (delayed) hypersensitivity. Analysis showed that, after adjustment for age, sex and socio-economic status, there was a positive and significant relation between the occurrence of immunologically related disorders (overall and the four types) and additional multimorbidity. This implies an increased disease susceptibility among subjects with an affected immunologic status.

The influence of genetics, although likely to be of interest, was not studied. Probably the relative contribution of genetics to disease has even increased in the last century, with more prosperity and better living conditions[18]. However, when this study was started, predisposing factors and genetic markers were rather obscure for all but a handful of conditions.

For the studies reported in this thesis, we focused on the influence of psycho-social and demographic characteristics on the occurrence of morbidity and multimorbidity. Selection of specific topics was based on a literature study and contacts with experts.

Of the 6,113 questionnaires sent, 61.3% was completed and returned. There were some indications for a selective non-response regarding the socio-demographic characteristics. It is hard to tell whether this has lead to over- or underestimation of the associations found. Regarding the amount and type of morbidity, there were very little differences between responders and non-responders. Only psychological disorders were more frequent among non-responders. This is reassuring: there were no indications for a biased non-response concerning

morbidity, and morbidity was one of the key measures in our studies.

Furthermore, a number of patients returned the questionnaire only partly completed. As much as possible questionnaires were completed by subsequent telephone interviews and by completion of subscales using directives to handle a limited number of missing items. Still, the various scales and items had 0% to 9% missing values. This was especially problematic when combining scales in multivariable models, because of case-wise deletion. Therefore dummy variables were defined in case of item non-response, to provide maximum use and precision of the data.

INTERPRETATION AND CONCLUSIONS

General remarks on interpretation

Although each of the empirical studies reported in this thesis leads to specific conclusions regarding characteristics associated with multimorbidity, a number of more general remarks can be made regarding the interpretation of the results.

The most important remark is about the nature and direction of the associations found. Starting with the exploration of associations, the final aim is to find causal relations. One of the most obvious conditions for a factor to be called causal is that it precedes the consequence. In case of multimorbidity research there is a couple of notices. First of all, multimorbidity is not an event that takes place at a single moment. Most of the time, patients first get one disease, some developing subsequent disease in the following time period. Furthermore, establishing the time of occurrence of diseases is complicated because the exact time of onset of diseases is often unknown: the registration of a disease on the problem list represents time of presentation of symptoms to the GP and the subsequent diagnosis by the GP. Because of these reasons, even in the cohort study it is difficult to be sure that the factors measured always preceded the multimorbidity found.

Furthermore, with an explorative study like this, it is not possible to measure all possible confounding factors and biases. Heterogeneities in registered health status may, for example, result from systematic differences in care-seeking behaviour, access to health services, or availability of other resources or characteristics that influence the effectiveness of care[19].

Interpretation of the results of the empirical studies

Throughout the empirical studies, previous findings regarding the influence of socio-demographic characteristics were confirmed. Moreover, increasing age is undoubtedly the most important risk factor for the occurrence of multiple diseases. The influence of sex as showing from our studies is less clear: whereas females were found to be less at risk for multimorbidity during follow-up, no relation was found in the case-control study and the analysis of the incidence rates in the total RNH population and an increased risk was found evaluating the prevalence rates of the total population of the RNH. Possible explanations include the addition of a selective group to the sample that was sent the questionnaire (500 controls aged 60 and older were added to the control group), or a selective non-response.

Taking into account the known - and hardly changeable - socio-demographic characteristics, we see a remarkable profile of psycho-social characteristics associated with the occurrence of multiple disease. From the results of our longitudinal study, a person most resistant to multimorbidity could be described as an initially young woman, living with a partner or family, and having a relatively large network of people to fall back upon. She would have an internal locus of control and a relatively large number of life events that are not labelled as positive or negative. In summary, she would be a self-assured person, well embedded in her social environment.

RECOMMENDATIONS

The main goal of this study was gaining insight in the prevalence rates, incidence rates and determinants of multimorbidity, using a broad nosological spectrum to enable the development of a risk profile, and to improve patient monitoring. Because of the nature of the factors found to be related, there are few direct possibilities to develop preventive interventions. Part of the factors found to be related are difficult or impossible to modify, like age and socio-economic status. The fact that socio-economic status is a persistent risk factor in many health studies should be motive (among many others) for a more balanced distribution of wealth.

Some of the psycho-social factors might be more receptive to change. There are for

example theories about the training of 'patient internality'[20]. Also in a field study with institutionalised aged persons, Langer and Rodin[21] showed that increasing the opportunities and expectations for controlling the environment had important consequences for health and feelings of well-being, as well as on mortality during a long follow-up period.

Also, a sufficient social embedding seems to be protective for the occurrence of multimorbidity. Previously, Noorthoorn van der Kruijff [22] suggested that therapy can provide protective factors, such as social support, that can act as a buffer. It is therefore advisable not only to motivate subjects with a small social network (and additional risk factors) to participate in networks, but also to offer them suggestions how to achieve this. It is important that the GP has good information about local societies and clubs, as well as information about patient unions and possibilities for contacts with fellow-sufferers. Brochures in the waiting-room or handed out by the GP can facilitate this. Furthermore, the GP should not only discuss the range of his patients' social network, but also the intensity and quality of the contacts.

For the daily work in general practice, this study provides few direct guidelines, although the health locus of control and the social network of patients' might give opportunities for interventions. Furthermore, this study has contributed to the development of a risk profile and gives the GPs a better understanding of patient groups that are at risk for multimorbidity.

In previous parts of this thesis we have hypothesised that psycho-social variables might be more strongly related to experienced health status or health related behaviour, than to health status as measured by the number of diagnoses at the GP's problem list. To test these hypotheses, we have planned additional analyses, using the self-reported mental and physical health as the outcome measure. Furthermore, a study has been started on the relationship between attendance rate with the GP and psycho-social and demographic characteristics.

Non-response increases the risk for bias. It is therefore of the utmost importance to minimise (item) non-response. Despite serious efforts a number of items from our questionnaire had a considerable amount of blanks. Although it increases the costs, it might be well worth the effort to do home or telephone interviews instead of postal questionnaires. This method gives a better opportunity to complete the questionnaires of responders, but might on

the other hand influence general response rates, and responders might be more apt to give less true, politically correct, answers in an interview than in a postal questionnaire. Another possibility is a combination of postal questionnaires and subsequent face-to-face or telephone interviews.

Given the results of previous research using a disease specific approach, we stress the importance of additional approaches focusing on person related factors. This factor specific research should include studies on e.g., psycho-social, immunologic, genetic, environmental factors. A combination of the results of disease and factor specific research might provide a more integral profile of patients at risk for multiple diseases, as well as patients at risk for specific (categories of) diseases.

To get more insight in causality and long-term effects of psycho-social variables on the occurrence of multimorbidity, we suggest developing studies with longer follow-up periods. Because of the possibility of characteristics changing over time, a repeated measurement of the psycho-social characteristics during the follow-up should be added.

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CHAPTER 9

SUMMARY

The general background, purpose and main questions of the studies reported in this thesis are described in *chapter 1*. The leading questions in the reported studies were:

- How can comorbidity and multimorbidity be defined and operationalized?
- What are the main relevant methodological and analytical issues with respect to research on comorbidity and multimorbidity?
- What are the incidence and prevalence rates of multimorbidity in the general population?
- What are the major determinants of multimorbidity, with specific focus on demographic and psycho-social and life style characteristics?

Chapter 2 contains a review of the literature on multiple pathology. There is a striking disagreement on the terminology and operationalization of co-occurring diseases. As a result, the different studies on this subject can hardly be compared. In order to diminish the lack of clarity we proposed to distinguish between two terms:

1. comorbidity with the original definition by Feinstein: 'Any distinct additional entity that has existed or may occur during the clinical course of a patient who has the index disease under study';
2. multimorbidity defined as: 'the co-occurrence of multiple chronic or acute diseases and medical conditions within one person'.

Other varying features of former studies concentrate on the type of diseases (e.g., acute, chronic), and the population being studied (e.g., general population versus hospital population, certain age categories).

Previous studies on the occurrence of multiple disease reported prevalences of multimorbidity varying between 1% to over 50%. Furthermore, some authors suggested causal relations between the occurrence of multimorbidity and a number of characteristics, but only a very few of these studies are empirical studies.

For an appropriate study of comorbidity or multimorbidity, it is important to make some explicit choices *(chapter 3)*:

- Is the study focused on comorbidity or on multimorbidity? This choice refers to the

distinction described previously; does the main research question concern diseases additional to one index disease (comorbidity) or the co-occurrence of diseases in general (multimorbidity)?

- Is it appropriate to exclude certain (types of) diseases for a particular study? The number and type of diseases (in particular differentiating between chronic and acute diseases) included in a study have a major impact on the prevalence and incidence rates of co-occurring diseases found and might also influence other relations under study.
- Especially relevant in comorbidity and multimorbidity research is the operationalization of diseases and disease entities; in specific studies it can be useful to define combinations of diseases that are pathophysiologically related as one disease. For other studies (e.g., measuring the number of complications of a certain disease), it might be more useful to count separate diagnoses. Furthermore, one has to realise that in multimorbidity research - covering a broad nosological spectrum - there are very few combinations that are exclusively related to one another and not to other diseases.

For the analysis of co-occurring diseases a number of strategies is available. Most commonly performed are descriptive measures of the prevalence rates of co-occurring diseases. Furthermore, there are methods to evaluate the statistical clustering of diseases at a population level, or at the level of subgroups of the population. The first method is based on a comparison of the actual (observed) and the statistically expected clustering. The observed clustering can either be expressed as the number or proportion of subjects with a specific combination of diseases or as the proportion of the population with none, one, two, three etc. of the diseases under study. The expected clustering can be calculated as the product of the separate prevalences, assuming statistical independence of the diseases. A ratio of the observed and expected clustering can then be calculated, expressing the amount of clustering beyond chance. Interpretation of this ratio might be difficult, because for many combinations of diseases the assumption of statistical independence is known not to be true. Still, the measure can be very useful, e.g. for comparison of the amount of clustering in different subgroups in the population.

Another method to evaluate clustering of diseases is the calculation of a relative risk or odds

ratio.

In *chapter 4* results of analyses of data from the Registration Network Family Practices (RNH) are reported. Using a broad nosological spectrum, we found a high prevalence of multimorbidity in the general population. Although increasing with age, the prevalence of multimorbidity was considerable among all ages, varying from 10% in the 0-19-year-olds to 78% in subjects aged 80 and older. In this large population, after adjustment for mutual relations, the prevalence of multimorbidity was found to be higher among females compared to males, increased with age, decreased with higher educational levels, was higher for subjects with public as compared to those with private health insurance, and was higher for subjects living in a home for the elderly compared to those living in a family.
The one-year incidence of multimorbidity in the RNH population was 1.3% overall. On average the number of new diagnoses was 0.11 per person, varying from 0.06 in young subjects (age 0-19) to 0.30 in the elderly (80 years and older). For the one-year incidence of multimorbidity, a higher risk was found for the elderly, subjects with a public compared to a private health insurance, and subjects who already had two or more diseases compared to those with no or only one prevalent disease. Statistical clustering of diseases was found for both sexes and all age categories, but decreased with age.

To evaluate the influence of other characteristics on the occurrence of multimorbidity 6,113 postal questionnaires sent out. Of those 3,745 (61.3%) were returned. Non-response analysis showed little differences between women and men, and between subjects with a pivate and public health care insurance. Non-response was higher among elderly (with the highest non-response among 60-69-year-olds), subjects living as a couple or in a family compared to those living alone, and subjects with a secondary or high educational level compared to subjects with a low educational level *(chapter 6)*. It is difficult to determine the direction and impact of possible bias resulting from this non-response on the relations between multimorbidity on the one hand and demographic, psychological and sociological characteristics on the other hand.
Regarding the amount and type of morbidity, there were very few differences between

responders and non-responders. Only psychological disorders were more frequent among non-responders. This is reassuring, morbidity being one of the key measures in our studies.

Evaluation of possible determinants was focused on psychological, sociological, life style and demographic features and was performed using retrospective data from a nested case-control study as well as from prospective data from the two-year follow-up.
Analyses of the retrospective data *(chapter 5)* showed that, apart from the known strong impact of age, socio-economic status and the number of prevalent diseases, multimorbidity was associated with few of the characteristics under study. Multimorbidity was more frequent among subjects who did not report (volunteer) work or study, subjects with an active coping style, those with a high occupational class and subjects with an external locus of control.
Analyses of the prospective data *(chapter 7)* were focused on the psycho-social factors. Characteristics found to be protective for the occurrence of new multimorbidity, as compared to morbidity, were: a high internal locus of control belief, the occurrence of life events of undetermined significance, living as a couple or in a family as compared to living alone, and a large social network.

In *chapter 8* the results of the various parts of this thesis are summarised and combined. The quality of the data used is discussed and it was concluded that both information from the Registration Network Family Practices regarding morbidity and patient background characteristics and data from the questionnaire were sufficiently valid and reliable. The choices made regarding operationalization of multimorbidity and the selection of determinants under study are described, and alternatives and consequences of these choices are discussed. At a more general level, the distinction between disease specific and factor specific aetiological research is commented.

CHAPTER 10

SAMENVATTING

In dit proefschrift worden verschillende studies beschreven die handelen over de incidentie, prevalentie en determinanten van multimorbiditeit.

In het *hoofdstuk 1* zijn de achtergrond, de aanleiding en de belangrijkste onderzoeksvragen beschreven. De hoofdvraagstellingen van de studies die in dit proefschrift beschreven zijn luiden:

- Hoe kunnen comorbiditeit en multimorbiditeit gedefinieerd en geoperationaliseerd worden?
- Wat zijn de belangrijkste methodologische en analytische thema's met betrekking tot onderzoek naar comorbiditeit en multimorbiditeit?
- Hoe hoog zijn de incidentie en prevalentie van comorbiditeit en multimorbiditeit in de algemene bevolking?
- Wat zijn de belangrijkste determinanten van multimorbiditeit, in het bijzonder demografische, psychologische en sociale factoren en levensstijl?

Hoofdstuk 2 bevat een literatuurstudie naar multiple pathologie. In onderzoeken naar het tegelijkertijd voorkomen van aandoeningen is er een opvallende discrepantie in het gebruik van terminologie en operationalisatie. Dit leidt ertoe dat de resultaten van de verschillende studies op dit gebied moeilijk direct met elkaar te vergelijken zijn. Om meer duidelijkheid te krijgen in de terminologie, stellen wij voor twee termen te onderscheiden:

1. comorbiditeit, volgens de originele definitie van Feinstein: 'een aparte, bijkomende entiteit die bestaat of optreedt bij een patiënt tijdens het klinisch beloop van de bestudeerde index-ziekte'; en
2. multimorbiditeit, gedefinieerd als: 'het tegelijkertijd voorkomen van twee of meer chronische of acute aandoeningen bij één persoon'.

Eerdere studies variëren met name ten aanzien van het soort aandoeningen (bij voorbeeld acuut of chronisch) en de studie-populatie (bij voorbeeld de algemene bevolking versus een ziekenhuispopulatie; bepaalde leeftijdscategorieën).

De prevalentie van multimorbiditeit, zoals gevonden in verschillende studies, varieert tussen 1% en meer dan 50%. Sommige auteurs noemen weliswaar mogelijke causale relaties

tussen het voorkomen van multimorbiditeit en bepaalde kenmerken, maar deze relaties zijn slechts zelden empirisch onderzocht.

Om comorbiditeit of multimorbiditeit goed te kunnen onderzoeken moet een aantal expliciete keuzes gemaakt worden *(hoofdstuk 3)*:

- Is de hoofdvraagstelling gericht op comorbiditeit of op multimorbiditeit? Deze keuze heeft betrekking op het eerder omschreven onderscheid: gaat de onderzoeksvraag over bijkomende aandoeningen bij een index-ziekte (comorbiditeit) of over het tegelijkertijd voorkomen van aandoeningen in het algemeen (multimorbiditeit)?
- Bij onderzoek van comorbiditeit of multimorbiditeit is met name de operationalisatie van aandoeningen en ziekte-entiteiten belangrijk; voor specifieke studies kan het zinvol zijn aandoeningen, die pathofysiologisch gerelateerd zijn, te combineren en te definiëren als zijnde één aandoening. Overigens moet hierbij wel opgemerkt worden dat bij onderzoek dat een breed nosologisch spectrum dekt, er weinig aandoeningen zijn die uitsluitend aan elkaar gerelateerd zijn en niet aan andere aandoeningen.

Er zijn diverse analyse-strategieën beschikbaar voor de evaluatie van tegelijkertijd voorkomende aandoeningen. Descriptieve maten, zoals de prevalentie van comorbiditeit/ multimorbiditeit, worden het meest gebruikt. Daarnaast zijn er methodes beschikbaar om de mate van statistische clustering van aandoeningen, op populatienivo of in subgroepen, te evalueren. De eerste methode om dit te evalueren is het vergelijken van de feitelijke (geobserveerde) en de statistisch verwachte clustering. De geobserveerde clustering kan uitgedrukt worden als het aantal of de proportie van personen met een specifieke combinatie van aandoeningen, of als de proportie van de populatie met geen enkele, één, twee, drie et cetera aandoeningen. De verwachte clustering kan berekend worden als het produkt van de afzonderlijke prevalenties, uitgaande van statistische onafhankelijkheid van aandoeningen. Vervolgens wordt de ratio van de feitelijke en verwachte clustering berekend, die de mate van clustering die niet aan toeval toe te schrijven is uitdrukt. Interpretatie van de ratio kan moeilijk zijn, omdat van veel combinaties van aandoeningen bekend is dat de aanname van statistische onafhankelijkheid niet klopt. Toch kan deze maat nuttig zijn, bij voorbeeld om de mate van

clustering in verschillende subgroepen te vergelijken.
De berekening van een relatief risico of odds ratio is een andere methode om de mate van clustering van aandoeningen te evalueren.

In *hoofdstuk 4* worden de resultaten van analyses van data van het RegistratieNet Huisartspraktijken (RNH) gerapporteerd. Gebruikmakend van een breed nosologisch spectrum, werd een hoge prevalentie van multimorbiditeit gevonden in de algemene bevolking. Hoewel de prevalentie toeneemt met de leeftijd, komt multimorbiditeit veel voor in alle leeftijdsgroepen, variërend van 10% in de leeftijdsgroep 0 tot 19 jaar tot 78% bij personen van 80 jaar en ouder. Na correctie voor onderlinge relaties, bleek de prevalentie van multimorbiditeit hoger voor vrouwen dan voor mannen, hoger bij ouderen, hoger bij een lager opleidingnivo, hoger voor ziekenfondsverzekerden dan particulier verzekerden, en hoger voor mensen die in een bejaardenhuis woonden dan mensen die in gezin of met partner wonen.
De 1-jaars-incidentie van multimorbiditeit in de RNH-populatie was 1,3%. Het gemiddeld aantal nieuwe diagnoses per persoon was 0,11, variërend van 0,06 bij jongeren (in de leeftijdsgroep 0 tot 19 jaar) tot 0,30 bij ouderen (van 80 jaar en ouder). Bij evaluatie van de 1-jaars-incidentie bleek een verhoogd risico voor ouderen, voor ziekenfondsverzekerden vergeleken met particulier verzekerden en voor personen die al twee of meer aandoeningen hadden in vergelijking met personen die geen enkele of één aandoening hadden. Voor zowel mannen als vrouwen en in alle leeftijdscategorieën werd statistische clustering van aandoeningen gevonden, maar deze nam af met stijgende leeftijd.

Voor het onderzoek naar de invloed van andere kenmerken op het ontstaan van multimorbiditeit werden 6.113 schriftelijke vragenlijsten verstuurd. Daarvan werden er 3.745 (61,3%) ingevuld en teruggestuurd. Uit de non-respons analyse bleken dat er weinig verschillen waren tussen vrouwen en mannen en tussen mensen met een particuliere ziektekostenverzekering en ziekenfonds verzekenrden. De non-respons was hoger bij ouderen (met de hoogste non-respons onder 60 tot 69 jarigen), wat hoger bij personen die in een gezin woonden dan bij alleenstaanden, en wat hoger bij personen met een middelbare of hoge

opleiding in vergelijking met personen met een lage opleiding *(hoofdstuk 6)*. Het is moeilijk te bepalen in hoeverre en in welke richting er door deze non-respons vertekening van de resultaten is opgetreden.
Ten aanzien van het aantal en soort aandoeningen van respondenten en non-respondenten werden zeer weinig verschillen gevonden; alleen psychiatrische aandoeningen kwamen bij de non-respondenten frequenter voor.

Het onderzoek naar mogelijke determinanten van multimorbiditeit was gericht op psychologische, sociologische, demografische en levensstijl-kenmerken en werd uitgevoerd met behulp van retrospectieve data uit een patiënt-controle studie en prospectieve data van twee jaar follow-up.
Uit de analyses van de retrospectieve data *(hoofdstuk 5)* bleek dat, afgezien van de sterke invloed van leeftijd, sociaal-economische status en het aantal prevalente aandoeningen, multimorbiditeit samenhing met enkele andere kenmerken. Multimorbiditeit kwam meer voor bij personen die noch (vrijwilligers)werk hebben noch studeren, personen met een actieve coping stijl, personen uit een hoge arbeidsklasse en personen met een externe beheersingsoriëntatie.
Analyses van de prospectieve data *(hoofdstuk 7)* waren gericht op psycho-sociale faktoren. Voor het optreden van nieuwe multimorbiditeit bleken de volgende factoren beschermend te zijn: een hoge interne beheersingsoriëntatie, het meegemaakt hebben van levensgebeurtenissen die noch als positief nog als negatief gekenschetst kunnen worden, leven in een gezin of met partner vergeleken met alleen wonen en het hebben van een groot sociaal netwerk.

In *hoofdstuk 8* worden de resultaten van de verschillende onderdelen van dit proefschrift samengevat en gecombineerd en worden de resultaten nader beschouwd. De kwaliteit van de data die gebruikt zijn wordt besproken en er kan geconcludeerd worden dat zowel de gegevens van het RegistratieNet Huisartspraktijken betreffende morbiditeit en patiënt-achtergrondgegevens, als de data verkregen door middel van schriftelijke vragenlijsten

voldoende valide en betrouwbaar waren. Keuzes die gemaakt zijn betreffende de operationalisatie van multimorbiditeit en de selectie van bestudeerde determinanten worden beschreven en alternatieven en de consequenties van gemaakte keuzes worden bediscussieerd. Meer in het algemeen, wordt het onderscheid tussen ziekte-specifiek en factor-specifiek onderzoek besproken.

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Marga van der Aa was onderzoeksassistent gedurende een groot deel van het project. Beste Marga, met veel plezier denk ik terug aan alle etiketten, stempels, vragenlijsten, postkantoren door heel Limburg en alles wat daarna kwam.
Sjef Roos, medewerker van de capaciteitsgroep Medische Informatica. Beste Sjef, er zijn tijden geweest dat ik bijna niet meer bij je aan durfde te kloppen. Veel van onze ideeën pasten niet in de standaardprogrammatuur. Dankzij jouw inzicht en inzet hebben we dingen kunnen doen waar we eerst alleen over droomden. Toch is Fortran voor mij nog steeds abacadabra.
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bovendien!).

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CURRICULUM VITAE

Marjan van den Akker werd geboren op 18 mei 1969 in Veghel. Het Atheneum A volgde zij aan het Mill Hill College te Goirle. Daarna studeerde zij Gezondheidswetenschappen aan de Universiteit Maastricht, afstudeerrichting Verplegingswetenschap, en volgde zij een aantal keuzevakken aan de Katholieke Universiteit Brabant en de Rijksuniversiteit Utrecht.

In 1992 en 1993 werkte zij als onderzoeksassistent bij de sectie Vrouwenstudies Geneeskunde en de capaciteitsgroep Epidemiologie van de Universiteit Maastricht. Eind 1993 startte zij als assistent in opleiding bij de capaciteitsgroep Huisartsgeneeskunde van de Universiteit Maastricht.

Momenteel is zij als onderzoeker aangesteld bij de capaciteitsgroep Huisartsgeneeskunde van de Universiteit Maastricht, en houdt zij zich bezig met onderzoek binnen het RNH (RegistratieNet Huisartspraktijken) en een onderzoek naar de rol van de huisarts bij ingrijpende gebeurtenissen.

APPENDIX

General practitioners participating in the Registration Network Family Practices during the study period:

Huisartsenmaatschap*
R.Leclerq, Ph. Govaert,
G.J. Dinant

Academische huisartspraktijk*
V. Zwietering

Gezondheidscentrum Heer
F. Vissers, G, Peeters, mw. A. Muysken

Gezondheidscentrum Dr. van Kleef*
B. Huijnen, P. Castermans, P. Stahlenhoef,
mw.M. Maaskant, B. Schilte

Gezondheidscentrum Hoensbroek-Noord*
G.J. van Schendel †, R. Helmers,
M. van Nunen, H. Paas,
mw. M. van Venrooy, P. Voorhoeve

Gezondheidscentrum Withuis*
P. Jansen, G. de Koning, H. van Dam,
H. Vlek, mw. T. van Kessel,

Medisch Centrum Putstraat
H. Ypma, J. Eussen, mw. C. Stuurman

Huisartsenpraktijk 'Grote Schuur'*
H.Schönberger, J. van Putten,
W. van den Broek

Huisartspraktijk*
M. op den Kamp, B. Maiburg

Huisartspraktijk*
B. de Wit

Huisartspraktijk Ubachsberg*
F. Guldemond

Huisartsenpraktijk*
P. Hulshof, R. Panhuysen, R. Constongs,
Y. Guldemond-Hecker

Huisartsenpraktijk*
V. Kaiser, J.W. Veldhuizen

Huisartspraktijk
H. van der Ploeg

Huisartsenpraktijk
F. Soomers, J. Soomers-Turlings,
J. Stoffers

*General practices participating in the case-control study